# Fertility Regulation

## From Laboratory Bench to Service Delivery

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**ABSTRACT OF SUBMISSION FOR A HIGHER DEGREE**

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The publications included in this thesis cover four broad areas of fertility regulation.

**Postpartum Contraception.** This section includes a number of studies investigating mechanisms underlying lactational amenorrhoea together with three studies investigating the relationship between infant feeding practices and the duration of amenorrhoea. A study on the effect of progestin-only oral contraception on bone mineral density during lactation and two studies on the timing and quality of advice about post-partum contraception complete this section.

**Modern methods of contraception.** A number of general reviews of modern methods of contraception are included in this section together with an overview of new developments and possible future methods. Original work includes studies on continuation rates of Norplant; acceptability of future methods (male and female): ovulation during the use of hormone replacement therapy; morphological and functional changes in the endometrium of women using low dose progestogen only methods and the use of antiprogestogens for various approaches to female contraception.

**Abortion.** The papers in this section concentrate mainly on service delivery issues including the establishment of a centralised referral system: audit of quality of care; counselling: acceptability and patient satisfaction.

**Emergency Contraception.** Original work on the efficacy and mode of action of emergency contraception; knowledge among teenagers; prevelance of chlamydia infection among women using emergency contraception (EC) and the need for de-regulation of EC are included in this section. The thesis ends with three studies on advanced administration of EC and its effect on use, risk taking behaviour and abortion rates.

The 66 publications I am submitting for the degree of DSc span 17 years of research which followed the work included in my MD thesis. The publications cover four main areas of research on fertility regulation - the contraceptive effects of breastfeeding, modern methods of contraception, abortion and emergency contraception. I have summarised the work in the introduction below referencing each publication in the text as it contributes to the theme. The publications are not therefore in temporal order.

## Fertility Regulation - From Laboratory Bench To Service Delivery

Introduction

Throughout history, mankind has tried to limit family size. Until the 19th century this was achieved by natural methods of fertility regulation including abstinence or infrequent intercourse; the avoidance of intercourse during the fertile period of the cycle; coitus interruptus and by breastfeeding. Male condoms were used primarily for the prevention of infection during that time.

### Postpartum Contraception

Breastfeeding is associated with a reduction in fertility. The demographic importance of the contraceptive effects of breastfeeding has been recognised for over half a century, but our understanding of the mechanisms underlying the effect of lactation on fertility stems from a body of work undertaken largely in the 1980s and 1990s, much of it in Edinburgh. A longitudinal study of the changes in the pituitary-ovarian axis accompanying the return of fertility in a cohort of women after childbirth was the subject of my MD thesis (1983). In women who do not breastfeed, follicle stimulating hormone (FSH) and prolactin (PRL) concentrations return to normal within four weeks of childbirth.[2] However, for normal ovarian follicular development, LH (luteinising hormone) as well as FSH, is required, [3,4] and in bottle-feeding women it is the return of a normal pulsatile pattern of LH secretion which determines the timing of the resumption of fertile cycles - usually within eight to ten weeks postpartum. The resumption of regular ovulatory cycles is substantially delayed if women breastfeed their babies, with the duration of infertility determined largely by the frequency of breastfeeding and the timing of the introduction of food other than breast milk. [5] Full breastfeeding is, at least initially, associated with complete suppression of ovarian activity and therefore with amenorrhoea. The suppression of ovarian activity is the result of a disruption of the normal pulsatile pattern of LH secretion.[6] It is assumed that the suckling stimulus directly inhibits the

release of hypothalamic GnRH [7] but, despite detailed investigation, the exact pathway through which suckling acts remains unclear. [8] Suckling is also associated with an acute increase in prolactin secretion [9] which is essential for the maintenance of lactation. Although it has been tempting to assume that prolactin per se is instrumental in maintaining lactational infertility, a precise link has been hard to identify. [10] Research using women with pathological hyperprolactinaemia as a model [11] supports the arguments against a direct role for prolactin inhibiting follicular development and ovulation. Nevertheless a simple disturbance in the pulsatile pattern of GnRH secretion may not by itself be enough to explain lactational infertility, since restoration of a normal pattern of LH pulses using physiological amounts of exogenous GnRH delivered by a pulsatile infusion pump [12] stimulates follicular development but does not restore normal ovulation. This is in contrast to the effects of such therapy in women with either pathological hyperprolactinaemia or hypogonadotrophic hypogonadism, in whom normal ovulatory cycles are restored.[13] Our understanding of the exact mechanism by which breastfeeding delays the resumption of fertility post partum is still incomplete.

Although the major role that breastfeeding has played (and still plays) worldwide in limiting population growth is well recognised, differences between infant feeding practices and their effect on the duration of lactational amenorrhoea had been the subject of limited scientific investigation. In 1989 the World Health Organization (WHO) Task Force on Methods for the Natural Regulation of Fertility embarked upon a large multinational study designed to explore the differences between populations in infant feeding practices, the duration of amenorrhoea and the risk of pregnancy. This large longitudinal study was undertaken in seven countries, five of them in the developing world, and involved detailed and prolonged follow-up of 4118 breastfeeding mothers and their babies. The study generated an enormous amount of data and the cohort of infants continues to provide evidence on the relationships between intra-uterine and early infant growth and future adult disease.

The findings from the WHO study [14,15,16] have confirmed that the duration of postpartum amenorrhoea is strongly linked to the breastfeeding stimulus but also that cross-cultural effects are also important. They also confirm that the lactational amenorrhoea method (LAM) is a viable approach to postpartum contraception with cumulative pregnancy rates during amenorrhoea ranging from 0.9% (95% confidence interval, CI = 0%-2%) to 1.2% (95% CI = 0%-2.4%).

Although breastfeeding still plays a major role in fertility regulation in many developing countries, it seldom features as a 'contraceptive choice' in developed countries. Since lactational amenorrhoea depends on frequent breastfeeding, in most parts of the world where women return to work outside the home soon after childbirth and are separated from their infants for intervals of eight hours or longer, LAM is not a very practical method of contraception for many women. In the UK many breastfeeding mothers rely on progestogen-only (which unlike combined hormonal contraceptives do not interfere with milk production), or barrier methods of contraception. Progestogen -only methods may offer an extra health benefit for lactating women since they appear to confer a degree of protection against the loss of bone mineral density which inevitably accompanies the hypo-oestrogenic state associated with lactational amenorrhoea.[17]

The WHO study further demonstrated that breastfeeding promotion and contraceptive advice to women after childbirth should be culture specific. Although women during pregnancy and the puerperium represent a captive audience for education and advice about postpartum contraception, countries, and programmes, vary widely in their interest in making use of the opportunity. In Scotland, despite a number of health professionals taking the opportunity to discuss contraception with women after childbirth, the advice given is often ill-timed, of poor quality and, in relation to breastfeeding, actually incorrect.[18] Although in the UK a considerable amount of pre-natal education takes place during the antenatal period, contraception is seldom discussed and the topic is left for perfunctory consideration after the baby is born. In a multi-country randomised controlled trial [19] we tested the hypothesis that expert,

individualized contraceptive advice given during the antenatal period would have an impact on contraceptive uptake, patterns of use and pregnancy rates during the first year after childbirth. Despite recruiting over 1600 women in centres in China (Shanghai), South Africa (Cape Town) and in Scotland (Edinburgh) we were unable to demonstrate any significant effect of the intervention. Pregnancy rates were determined by the inherent effectiveness of the contraceptive method chosen rather than by the quality or timing of advice.

**Modern methods of contraception**

During the 19th century barrier methods of contraception for use by women and the intrauterine device were developed and continue today to provide contraception for millions of women worldwide.[20] In the United Kingdom hormonal contraception, including combined and progestogen only methods, is currently the most popular method of fertility regulation.[21,22] The combined oral contraceptive pill was introduced in 1960 and much of contraceptive research, at least by the pharmaceutical industry, has been and still is dominated by minor changes in the steroid hormone recipe for 'the pill.' [23] The 1990s saw the introduction and increasing uptake of long acting progestogen-only methods of contraception including implants [24,25] and the hormone-releasing intrauterine system LNG-IUS.[26] The latter method is particularly attractive to older women [27] since it is highly effective, lasts for five years and is associated with a reduction in menstrual bleeding at a time of life when menstrual dysfunction is becoming common. It can be combined with exogenous oestrogen for women in the perimenopause who still require contraception but begin to experience vasomotor systems and wish to take hormone replacement therapy (HRT). Unlike conventional oral HRT which is not reliably contraceptive[28], the LNG-IUS provides highly effective contraception while simultaneously protecting the endometrium from the potentially neoplastic effects of unopposed oestrogen. Contraceptive implants are as effective as female sterilisation [29,30] but have the advantage of being reversible.

While a broad range of contraceptive options is presently available, none are perfect and rates of discontinuation can be high, even for methods which have to be removed by a health professional should the user wish to stop using it.[31] One of the commonest reasons for discontinuation of all hormonal methods of contraception is so-called unscheduled bleeding.[32] Irregular and unacceptable endometrial bleeding is particularly common with low dose progestogen only methods of contraception. Although our understanding of the morphological and functional changes in the endometrium of women using these methods is improving, [33,34,35] we are still a long way from finding a strategy - other than changing to a different contraceptive method, or adding oestrogen - to solving the problem. One solution may be the addition of an anti-progestogen which might improve bleeding patterns, either through a direct effect on the endometrium or by inducing ovulation. [36] In a double-blind, randomised placebo-controlled trial involving 100 implant users in China once/month administration of mifepristone has been shown to improve bleeding patterns. [38]

Antiprogesterones indeed represent the most exciting advance to date in the development of new methods of contraception. [38] Although currently licensed in the developed world only for the induction of abortion, the anti-progesterone mifepristone has been shown to be effective as a contraceptive when given daily, once weekly, once per month [39] and post coitally.[40]

New methods of contraception, if they are to be widely used, must be acceptable to the men, women or couples for whom they are intended. The theoretical acceptability to women of a pill which need be taken only once a month (and then only if intercourse has occurred) seems obvious and has indeed been demonstrated in a number of developed and developing countries.[41,42] Less predictable, and indeed commonly regarded as being somewhat unacceptable, particularly in developing countries, is the concept of a method of contraception which is associated with amenorrhoea. Although a large multinational study undertaken by the World Health Organization in the 1980s strongly suggested that women preferred to have regular

menstrual bleeding, more recent work suggests that amenorrhoea is becoming acceptable - even desirable - even in the developing world. [43] Yet more controversial is the potential acceptability of hormonal contraception for men. Despite decades of research into a 'male pill', many opinion makers have suggested that most men would be reluctant to use a 'pill' and that in any case women would not trust them to take it reliably. Multicentre studies of men [44] and women [45] undertaken in China, Hong Kong, South Africa and Scotland demonstrated that there would be a market for hormonal contraception for men and that women, while they may not trust men in general, would trust their own partner to use it. Women felt strongly that men should take more responsibility for the regulation of fertility than they currently do.

Whoever does take responsibility for contraception, incorrect or inconsistent use as well as method failures will contribute to the burden of unintended pregnancy. Poor compliance probably accounts for the majority of contraceptive failures but is extremely difficult to measure. [46] When failure occurs women must have access to abortion.

**Abortion**

Abortion is an intrinsic part of fertility regulation, indeed it is almost impossible for a country to achieve a low fertility rate without recourse to abortion. The UK is no exception, with a total fertility rate in 2000 of 1.7, around 1 in 5 pregnancies end in abortion. Therapeutic termination of pregnancy is a core service provided by the National Health Service.[47] The availability and accessibility of abortion services varies widely in the UK but in general are well organised in Scotland.[48] The establishment of a centralised referral system[49] which we described in 1991 reduces the time women have to wait to have their abortion and is now recommended as standard practice. Scotland's abortion services were audited nationally in 1993 [50] using criteria for good quality care agreed nationally by the consultant body.[51] Two thousand and four patient episodes of abortion care were reviewed in two rounds of audit, the second taking place after recommendations for change - arising from the results of the first round - had been disseminated. Increased availability of medical

abortion was one of the major improvements demonstrated in the management of induced abortion. In 1994 57% of women seeking abortion in Edinburgh who were eligible to do so chose a medical procedure in preference to surgical abortion [52] and this trend has continued

In Scotland the majority of women are satisfied with the care they receive while undergoing induced abortion.[53] They receive adequate emotional support and counselling [54] and appreciate the opportunity to choose between medical and surgical abortion.[55] One of the few failings of the organisation of abortion services in Edinburgh (and elsewhere in Scotland) is the provision of appropriate contraception post-abortion. We are presently undertaking a cluster randomised trial to determine the effect of offering individualised expert contraceptive advice, provision and follow-up to a cohort of women undergoing induced abortion to determine the effect on contraceptive method chosen and continuation rates.

**Emergency Contraception**

Many unintended pregnancies could be prevented by the use of emergency contraception even if unprotected intercourse does occur. Emergency contraception (EC) is estimated to prevent between 60 and 85% of pregnancies.[56,57] It has been licensed in the United Kingdom since 1984.[58] Although we are still not entirely sure how it works [59,60], it is extremely safe.[61] It must be used within 72 hours of intercourse and is probably more effective the sooner it is used. For this reason it was argued for much of the 1990s that it should be made available without the need to see a doctor.[62] EC was eventually taken off prescription in the UK in 2001 improving accessibility. This should improve its use particularly among teenagers who are well informed about it [63] but who have a tendency to lead somewhat risky sexual lifestyles.[64] Even availability 'over the counter' may not increase the use of EC sufficiently to make an impact on abortion rates since at £24.99 per course (in 2003), it is extremely expensive and women still need to be motivated to go and buy it. A potentially better solution is to provide women at risk of unprotected intercourse or contraceptive failure with a supply of EC to keep at home so that it can

be used every time it is needed. A pilot study [65] undertaken in Edinburgh demonstrated the safety of this approach and suggested that it may reduce unwanted pregnancies. A much larger community based study involving over 17,000 women living in Lothian has now been completed and the results are in press. The initiative made no significant impact on abortion rates [66] despite quite promising patterns of use by the women who had a supply to keep at home. [67] The most likely explanation for the failure of advanced provision of EC to influence abortion rates lies in the observation that many women simply do not recognise that poor use of contraception puts them at risk of pregnancy and so, even despite having a supply of EC, they do not use it. If abortion rates in the UK are to be reduced by interventions aimed at increasing contraceptive use perhaps a major effort needs to be made to encourage the use of methods which are less dependent on compliance.

**DECLARATION**

This dissertation includes 67 publications the majority of which were written in collaboration with others. The single author book chapters [20, 22 and 29] and the more scholarly reviews [1, 23, 24, 26, 56, 57 and 62] were written solely by myself. The reviews on lactation and lactational amenorrhoea [2, 5, 7 and 9] were written by Alan McNeilly and myself, and incorporated data generated by me. The joint reviews authored with David Baird [21, 32 and 38] , Ailsa Gebbie [27] and Evert Ketting [58] were written by a process of dividing the review into sections and allocating primary responsibility for each section to the most appropriate author, with all authors reviewing the final version.

The review articles on abortion [47,48,54,55] covering issues of serviced delivery were authored solely by me. I conceived the proposal to audit the centralised abortion referral service [49], collated much of the data and wrote the manuscript. I contributed to the data collection and reviewed the manuscript of the paper on trends in abortion management in the Royal Infirmary of Edinburgh [52

Four papers [50, 51, 53 and 30] were funded by the Gynaecology Audit Project in Scotland. As a member of the Steering Committee for the project I participated in the design and organisation of the study and had a major role to play in reviewing the manuscripts.

Eleven of the papers [17,18, 25, 28, 31, 41, 60, 63, 64, 65 and 66] report the findings of research projects conceived by myself. I wrote the protocol for the studies, obtained funding [where relevant], oversaw the day to day running of the project and had a major part in writing them up. The study reporting the use of Mifepristone for emergency contraception [40] was conceived by David Baird, we jointly designed the

protocol and obtained funding while I oversaw the running of the trial and wrote the paper.

The final paper in this thesis [67] reports a study undertaken in collaboration with the University of Edinburgh Department of General Practice. The study – which forms part of the Lothian Emergency Contraception project – was my idea. With Karen Fairhurst and Sally Wyke I wrote the grant proposal. The authors of the paper met regularly to discuss the design and progress of the study and analysis of the results. Pete Seaman did the interviews supervised by Karen Fairhurst who oversaw the day to day running of the project and wrote the first draft of the paper.

Four papers on the mechanisms underlying lactational infertility [6,8,10,11] report the result of studies funded by a grant from WHO [held jointly with Dr Alan McNeilly]. Clem Tay is the first author of all four papers, I prepared the grant application, supervised the clinical aspects of the study and had a major input into writing the manuscript.

The studies on the role of FSH and pulsatile secretion in follicle development in both lactating women [12] and women attending infertility or reproductive endocrine clinics [3, 4, 13] were undertaken by myself in collaboration with Professor Baird and others. I recruited the subjects, collected the samples, monitored the therapy, undertook most of the ultrasound scans and wrote the manuscripts.

The three WHO studies [14, 15, 16] are credited to the Task Force on Methods for the Natural Regulation of Fertility. I was a member of the steering committee of the task force from 1985 until 1994. I chaired a subgroup of four task force members responsible for designing the study and monitoring its progress and undertook site visits to three of the participating centres and to two other centres which ultimately did not take part. The task force met twice a year to monitor the study. I spent four weeks at WHO in Geneva collating the data and writing the first draft of all three manuscripts.

Three studies on the morphological and functional changes in the endometrium of women using low dose progestogen only methods of contraception were done in collaboration with Hilary Critchley [33,34,35]. I had a major role in designing the studies, undertaking clinical supervision of the project and writing the manuscripts. The two papers [36 and 37] on the effects of adding Mifepristone to Norplant to reduce irregular bleeding were my idea. I wrote the protocol, oversaw the day to day running of the study undertaken in Edinburgh, and wrote both the papers.

Eight research projects were funded by the Contraceptive Development Network [19,39,42,43,44,45,46,59]. The work was supported by a grant from the MRC and DFID. It was my idea to use the modified Persona to time ovulation and to measure ovarian activity in the studies described in papers 39, 46 and 59. I jointly designed the protocol for the studies with David Baird, oversaw the day to day running of the projects and had a major role in writing the papers. The study on postpartum contraceptive advice for antenatal women was my idea, I wrote the protocol and had a major hand in writing the final paper. For all of the other CDN studies, the data were collected by a variety of clinical research fellows or nurses, Karen Smith oversaw the day to day running of the projects but I had a major hand in writing the protocols, analysing the data and writing the manuscripts.

All co-authors have given their permiss on for papers which they have co-authored to be included in this thesis.

Signed:

Date: 1.1.04

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historical perspective

# Contraception – past and future

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**Modern contraceptive methods have a surprisingly short history and are dominated by the oral contraceptive pill, which came on to the market in 1960. New developments since the advent of the pill have been largely limited to tinkering with the contents and routes of administration of hormonal contraception. The knowledge that would allow a more exciting approach to new contraceptives does exist but the will to proceed is hampered by financial, political and moral factors, and perhaps ironically by the AIDS epidemic.**

Throughout history, mankind has tried to limit family size. Until the last century, this was largely achieved by behavioural modifications, including abstinence, infrequent coitus, the avoidance of intercourse during the fertile period of the cycle and coitus interruptus (the withdrawal method). In population terms, breast-feeding, which inhibits normal ovarian activity, has been one of the most important means of limiting fertility, whereas for individual couples, coitus interruptus – first mentioned in the book of Genesis – has had a major role to play. One artificial method of contraception, the condom, has a surprisingly long history. Penile sheaths were described in Egypt in 1350 BC. Originally made from animal intestines, and later from linen or silk, they were used mainly for protection from venereal disease. Not surprisingly, given the place of women in society, female barrier methods arrived much later on the contraceptive scene. The first 'womb veil' is attributed to an American working in the early 1800s and the first cervical cap was produced in Germany around 1830. It took more than 150 years before the female condom[1] came on to the market in 1993.

## The intrauterine device

Until the second half of the 20th century, the only other artificial method of contraception was the intrauterine device (IUD). It was first developed in 1909 in

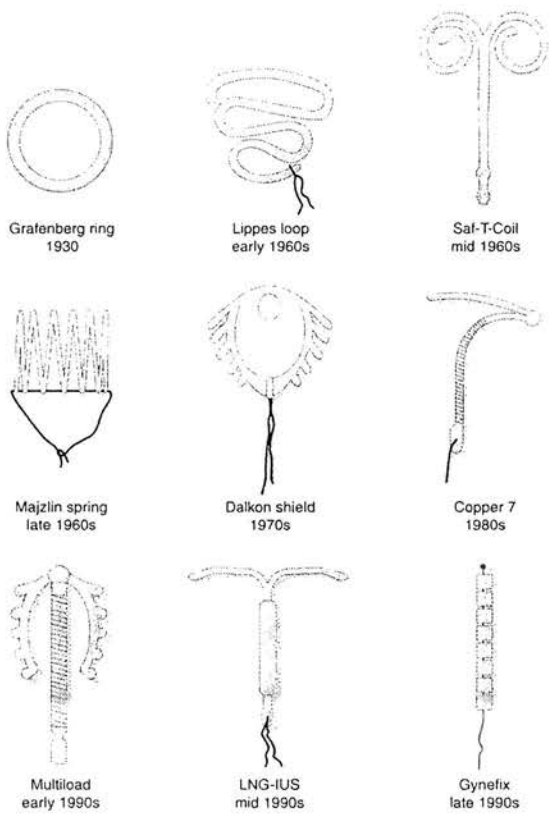


Figure 1 **Intrauterine devices through the 20th century.** Dates represent roughly the time of first availability in the UK or USA.

Germany from loops of silk-worm gut, later from silver–copper alloys and eventually from plastic (Fig. 1). The modern IUD appeared in 1969 when copper was added to the plastic frame, improving contraceptive efficacy and allowing the size of the device to be reduced[2]. Most recently, the plastic frame was removed in the belief that side-effects will be reduced through use of an even smaller device (Fig. 1)[3]. IUDs fell into disrepute in the mid-70s when a rather fearsomely shaped device with a multifilament tail – the Dalkon Shield – was shown to be associated with pelvic infection and infertility[4]. Nevertheless the IUD is one of the most commonly used methods of contraception in the world, thanks mainly to widespread use in China. Despite being highly effective, extremely safe, long-acting (IUDs are licensed for 5–10 years of use) and very cheap, the copper IUD is not popular in the USA, nor in much of Western Europe.

## Advent of the oral contraceptive pill

The advent of the oral contraceptive pill, developed by Pincus and Rock and colleagues[5] and first marketed in 1960, heralded a revolution in contraception and arguably laid the foundations for women's liberation. Perhaps the most widely researched drug in the history of therapeutics, the pill has been repeatedly shown to be safe and effective[6]. It has been, and remains, a favourite subject of media hype, and despite its safety record, the majority of women still perceive the pill as potentially dangerous[7]. It is of course statistically much safer than pregnancy.

## Developments in oral contraception

Much of the very recent history of contraception centres round hormonal methods. In the first two decades after the pill was marketed, research efforts were concentrated on improving safety and reducing side effects. This was achieved by lowering the dose of oestrogen (ethinylestradiol) and experimenting with different types of progestogen. The dose of estrogen has been reduced from 150 μg to 20 μg, and a pill containing 15 μg is currently in clinical trials[8]. Nervous of compromising efficacy with such a low dose, investigators have tried reducing the duration of the pill-free interval from the traditional seven days to four or five days and substituting the placebo tablet or pill-free day with a small dose of estrogen alone[9]. Biphasic and triphasic regimens (in which the dose of hormones changes two or three times throughout the 21 days of treatment) were introduced in an attempt to improve bleeding patterns and safety by mimicking the normal physiological cycle. These regimens have never proven better than monophasic pills and are indeed more complicated and more expensive.

"The advent of the oral contraceptive pill... heralded a revolution in contraception and arguably laid the foundations for women's liberation."

Most of the efforts with new progestogens have centred around producing less androgenic compounds. Ironically, this may have resulted in a slightly increased susceptibility to venous thrombosis and a marginal reduction in safety, resulting in the pill scare of 1995 (ref. 10). Drospirenone, the most recent progestogen to reach the market, has anti-mineralocorticoid properties that are reported to reduce fluid retention[11]. Heralded by the media as the pill which "makes you lose weight", rumour has it that supplies were sold out after only one month of this pill coming on to the market in Germany.

## New routes of administration

Although the pharmaceutical industry still seems pre-occupied with the dose and type of steroids, research into hormonal contraception in the last twenty years has concentrated on the development of new delivery systems. Avoiding the oral route has the theoretical benefit of bypassing the first pass of metabolism through the liver and providing constant release rates of steroids. It has the very real benefits of reducing or eliminating the need for compliance and increasing choice. Injectable progestogens (depot medroxyprogesterone acetate and norethindrone enanthate) were approved in some countries in the early 1980s. Combined injectables (containing both estrogen and progestogen and administered monthly[12]) are now widely used in Central and South America and have recently been approved in the USA. Progestogen-only contraceptive implants became widely available in the 1990s. Initially marketed as six silicon-rubber-coated rods that were implanted subdermally in the upper arm (Norplant), the number of rods was reduced to two (Norplant 2, Jadelle) and finally to one (Implanon)[13]. Implanon lasts for three years and to date no method failures have been reported. The addition of a progestogen to the intrauterine device has produced an IUD that is licensed for 5 years, but which, in contrast to the copper IUD, is associated with a significant reduction in menstrual bleeding (Fig. 1, LNG-IUS)[14]. The concept of a five-year contraceptive that dispenses with menstrual periods is extremely attractive to many women in Europe. In the UK for example, the levonorgestrel-releasing device presently accounts for 11% of the hormonal contraceptive market. At the end of this long list of new delivery systems comes the contraceptive vaginal ring[15] (worn in the vagina for 21 days and removed for 7 days) and a contraceptive trans-dermal patch[16]. Both contain ethinylestradiol in combination with a progestogen and both will become available in the USA during 2002. Lagging behind (estrogen replacement therapy for menopausal women is already available in both forms) is the development of a trans-dermal gel and trans-nasal spray delivering contraceptive

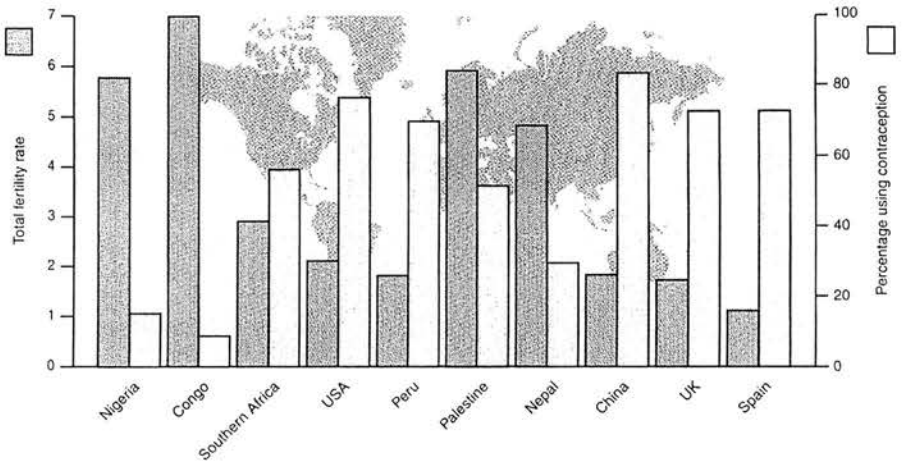


Figure 2 **Percentage of married/cohabiting women of reproductive age using contraception and average family size[28].**

hormones. If and when these become available, all the different routes of administration of hormonal contraception will finally have been exhausted and perhaps technology will move on to something that is radically different.

## Health benefits of contraception

The idea that contraception can be used not only to prevent pregnancy but also to confer health benefits, and particularly to reduce the frequency of menstrual bleeding, has received considerable interest in the last couple of years. However, this hypothesis is not new. It was demonstrated in the early 1970s in Scotland[17] that women could, and would like to, run packets of oral contraceptive pills together, allowing a three-monthly, rather than a monthly, withdrawal bleed. The idea has recently been rediscovered in the USA, where in 2002, a three-monthly combined oral contraceptive pill (Seasonale, Barr Laboratories, NJ) is in clinical trials.

The potential for additional health benefits may restore the enthusiasm of pharmaceutical companies for contraceptive research. The use of selective oestrogen receptor modulators (SERMS), for example, to develop a contraceptive pill that reduces the risk of breast cancer must be very tempting.

## Future prospects

Although contraceptive development seems to have almost ground to a halt with regard to steroid hormone methods for women, some exciting work has been undertaken on some different technologies. The feasibility of hormonal contraception for men has been recognised for more than fifty years[18]. It is, after all, based on the same concept as the pill. A variety of regimens have been tested, most of them (and probably the first to reach the market) comprising a progestogen to suppress spermatogenesis, combined with testosterone replacement to maintain sexual function[19]. The long delay in the development of a hormonal method for men is due partly to the lack of an appropriate long-acting form of testosterone replacement, but also to the commonly held belief that 'men would never use it' and women would never trust them to take it[20]. Although contraception is still very much seen as the responsibility of the woman, particularly in developing countries, recent surveys of men and women in Scotland, China, Hong Kong and South Africa suggest that a male pill would have a significant place in contraceptive choice[21,22]. Lured by the potentially huge market of testosterone replacement therapy for ageing men, the pharmaceutical industry has at last made some, albeit not absolutely wholehearted, commitment to the development of hormonal contraception for men.

Immunocontraception also seems to have been in the pipeline for a disproportionate length of time. Vaccination against the egg (specifically the zona pellucida), sperm and embryo (specifically β human chorionic gonadotropin) are all technically possible[23]. However, progress has been hampered by a variety of factors, including uncertainty about the long-term effects of immunizing against human tissues, and fears, perhaps ironically from women's groups, that contraceptive vaccines too easily lend themselves to coercive family planning policies.

Perhaps the greatest promise for a radically new method lies with the use of antiprogesterone. Orally active and effective as a daily[24] or once-a-month pill[25,26], the antiprogesterone mifepristone is now marketed in China as an emergency contraceptive[27]. Elsewhere in the world, its development has been seriously inhibited by the anti-abortion lobby, because the

principal use of mifepristone is as an abortion pill. The saga of mifepristone illustrates the difficulties that almost every advance in contraception has encountered. It may seem obvious, but contraception cannot be separated from sex, and everyone is interested in sex. Thus, in contrast to, say, anti-hypertensive drugs, everyone tends to have a view on contraception. Contraception is also inextricably bound up with social, cultural, moral and religious factors that often influence, if not the availability of methods, certainly their accessibility. The increasing tendency towards litigation, which even if unsuccessful, is extraordinarily expensive and time-consuming, has also served as a damper on the development and availability of new methods. All these influences make the pharmaceutical industry nervous when it comes to taking on new leads.

## Impediments to contraceptive development

In recent years, research progress has depended largely on not-for-profit organizations, such as the World Health Organisation and the Population Council. However, two significant factors have had a major effect on even their enthusiasm to develop new methods. The first is the HIV/AIDS epidemic. Although it led to the renaissance of the condom and a renewed interest in the development of better barrier methods, albeit with limited scope for much improvement, it has undoubtedly reduced the interest in developing other new methods of contraception. This is partly because funds and research efforts have been sidetracked into developing microbicides, but also because of the commonly-held view that it is bordering on the 'unethical' to work on new methods of contraception that do not simultaneously prevent HIV transmission.

The second major impediment to contraceptive development has been the widespread view that the population problem has been solved, with the result that donors no longer regard contraceptive research as a priority. It is indeed true that in the thirty years between 1965 and 1995 the total fertility rate (TFR) in the world fell from 4.9 to 2.8 children per woman and that in 1997, 51 countries – accounting for over 44% of the global population – had fertility rates below the replacement level (2.1)[28]. However, the TFR in most countries of the African continent is over 5.5, and in these same countries less than 20% of married women are using contraception (Fig. 2)[28]. Despite higher contraceptive prevalence, abortion rates continue to rise in most countries worldwide, including the developed world, and unwanted and mis-timed pregnancy accounts for tens of thousands of maternal deaths each year.

As more and more women start having sex at an earlier age, delay childbearing for longer and have smaller families, many of them are destined to use contraception for more than thirty years. Most women will do almost anything to avoid an unwanted pregnancy and presently tolerate the inconvenience, side effects and albeit small risks of currently available methods. Many live in countries and have lifestyles that do not put them at risk of HIV, and in any case many would be prepared to use a method of contraception while at the same time using something else which prevents infection. Modern scientific methods can now identify genes whose products are solely involved in reproduction and which are therefore prime targets for the inhibition of conception[29]. We have the wherewithall to produce much better methods of contraception. It seems extraordinarily complacent to expect people to settle for second-best. ❑


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# Maternal Nutrition and Lactational Infertility

Editor

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# Endocrine Control of Lactational Infertility. I

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Although there is no doubt that breastfeeding suppresses ovarian activity, the reasons for the immense variability in the duration of this suppression and the mechanisms by which the suckling stimulus causes it remain unclear. The interbirth interval in women who breastfeed can be divided into three main components: (a) the period of lactational amenorrhoea, (b) a period when menstruation returns either during or after lactation, and (c) pregnancy. The length of periods a and b will vary considerably depending on the pattern of breastfeeding, and in a few cases pregnancy will occur during the period of lactational amenorrhoea without an intervening period of menstrual cycles. In an attempt to clarify the mechanisms controlling each of periods a and b above, the changes in endocrine and ovarian activities will be explored.

## GONADOTROPHIC CONTROL OF THE MENSTRUAL CYCLE

Before discussing in detail the influences of suckling on ovarian activity, it is first necessary to outline the basic mechanisms controlling the growth and development of follicles and subsequent formation of the corpus luteum in the normal menstrual cycle. The basic changes in the four principal hormones involved are shown in Fig. 1.

At the time of menses following the demise of the corpus luteum of the previous cycle, follicle development starts, and usually a single follicle begins to grow. This growth is initiated by the pituitary gonadotrophin follicle-stimulating hormone (FSH). The continuation of growth, although requiring the continued presence of FSH, is dependent on oestradiol secreted from the growing follicle in response to luteinizing hormone (LH). LH is released in a pulsatile manner from the pituitary, the frequency of these pulses increasing through the follicular phase of the cycle. This increase in LH-stimulated oestradiol secretion, together with the continued stimulation of FSH, stimulates follicle growth and increased oestrogen secretion. Around midcycle, when the single dominant follicle is approximately 18 to 22 mm in diameter, the increase in oestradiol secretion is sufficient to trigger the release

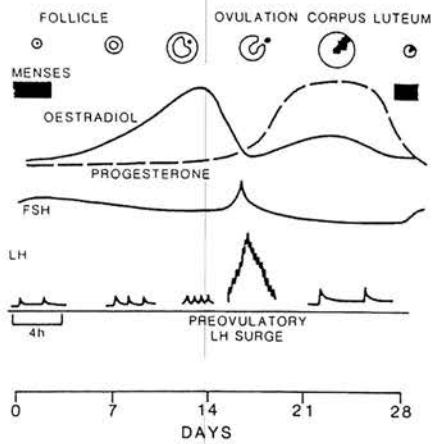


**FIG. 1.** Schematic diagram of the endocrine changes during the menstrual cycle. Note that the initial growth of the follicle is due to an increase in FSH around menstruation, whereas continued follicle growth occurs in response to oestradiol. This is secreted by the follicle in response to pulses of LH, the frequency of which increase towards midcycle. The increase in oestradiol triggers the preovulatory surge of LH, which induces ovulation, and transformation of the follicle into the corpus luteum, which secretes progesterone.

of the preovulatory surge of LH and FSH. This temporarily inhibits ovarian steroid secretion, alters the steroidogenic machinery of the follicle to make it secrete predominantly progesterone (luteinization); and some 36 hr after the start of the LH surge, ovulation occurs, with the oocyte being ejected from the follicle. The follicle then collapses and forms the corpus luteum, which, under the influence of LH, secretes progesterone and oestradiol (Fig. 2).

Of critical importance to this sequence of events is the maintenance of LH secretion in the follicular phase of the cycle. As mentioned above, LH is released in a pulsatile manner from the pituitary. This occurs as a result of pulsatile release of gonadotrophin-releasing hormone (GnRH) from the hypothalamus, reaching the pituitary gland via the hypophysial portal blood system.

While the overall controller of GnRH release remains to be determined, it is sufficient to think in terms of a hypothalamic GnRH pulse generator, the frequency of which is modulated by the ovarian steroids. Thus, oestradiol appears to increase the GnRH pulse secretion, whereas progesterone and oestradiol decrease pulse release.

In many amenorrhoeic states pulsatile secretion of LH, which can be measured, is abnormal, either slow or absent. Many of these states can be treated by pulsatile infusion of GnRH delivered subcutaneously or intravenously by a minipump worn by the patient.



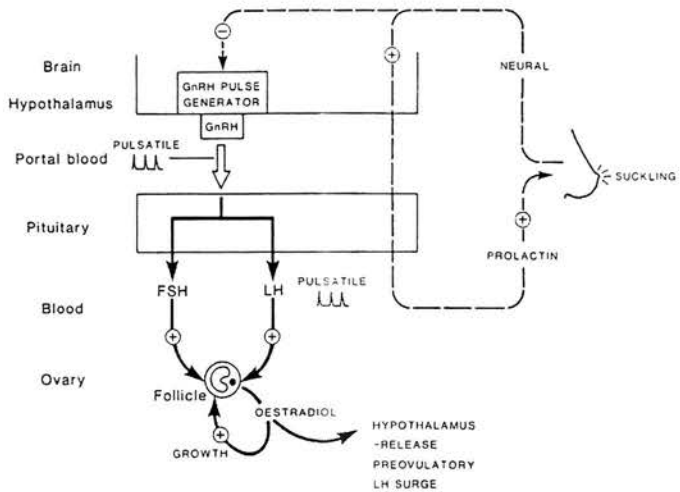


**FIG. 2.** Schematic diagram of the hypothalamic control of gonadotrophin secretion. Note that GnRH is released in pulses from the hypothalamic pulse generator and induces pulsatile LH release from the pituitary. The subsequent sequence of events in terms of follicle development is outlined in Fig. 1. It is envisaged that suckling either via a direct neural input and/or by increasing prolactin secretion alters the frequency of LH pulse secretion by affecting the hypothalamic GnRH pulse generator.

In lactation a similar alteration in the pulsatile secretion of GnRH has also been identified, suggesting that the principal site where suckling affects ovarian activity is at the hypothalamic GnRH pulse generator.

## LACTATIONAL AMENORRHOEA

### Recovery from Pregnancy

During pregnancy, the high circulating plasma levels of placental steroids suppress pituitary levels of both LH and FSH to approximately 1% of normal (1), whereas the increase in oestrogen secretion substantially increases the number of lactotrophes in the pituitary and plasma levels of prolactin (2). Following parturition and the clearance of these steroids, pituitary and plasma prolactin levels decline, and plasma levels of FSH and LH increase within 30 days in a non-breastfeeding woman (3–5). This resumption of the pulsatile secretion of LH (6) leads to an early return of follicle growth and menstruation, although first menstruation is usually preceded by an inadequate (80%) or absent (20%) luteal phase in terms of pregnanediol secretion (7). Luteal function subsequently improves, so that by the third

postpartum cycle, normally between 70 and 120 days postpartum (8), the majority of cycles (88%) have normal luteal function (7).

Thus, the delay in the resumption of normal ovulatory cycles in non-breastfeeding women depends mainly, if not exclusively, on the time taken for the recovery of the hypothalamo-pituitary-ovarian axis from the suppressive effects of pregnancy.

### Suppression of Ovarian Activity

The results in non-breastfeeding women suggest that even limited corpus luteum function will result in the recurrence of menstruation. Thus, it can be assumed that during lactational amenorrhoea ovarian activity is sufficiently suppressed that ovulation normally does not occur. Assessment of follicular development either in terms of plasma levels of oestradiol (3–5) or total urinary oestrogen (8–10) confirm that follicular development rarely occurs during lactational amenorrhoea (Fig. 3). More recently we have confirmed by ultrasound the absence of medium- or large-sized follicles within the ovary in breastfeeding women (11). However, although urinary oestrogen levels are below those which would indicate follicular development equivalent to that seen around day 5 to 7 of the normal menstrual cycle, we have recently observed, by estimation of urinary oestrogens in daily early morning urine specimens, that there may be periods during which follicle growth is initiated, indicated by a rise in oestrogen, but not sustained.

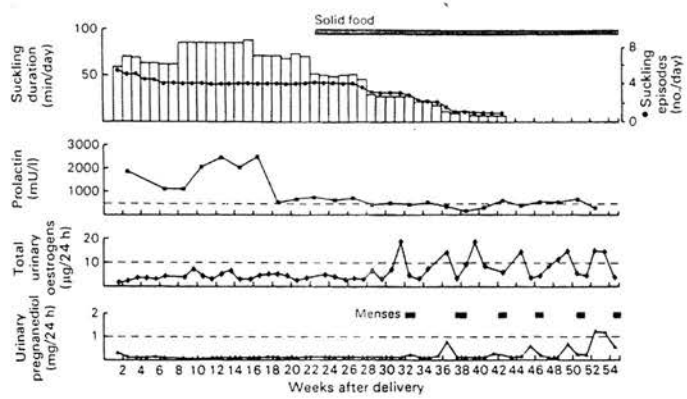


**FIG. 3.** Changes in urinary total oestrogens and pregnanediol in relation to the suckling frequency and duration and plasma levels of prolactin in a breastfeeding woman. Note that even at four feeds each day with a suckling duration of 50 min/day, follicular development in terms of oestrogen is below the lower limit of normal (10 μg/24 hr), whereas prolactin remains at or above the upper limit of normal (500 mU/liter). First menstruation is not preceded by ovulation, and the four subsequent cycles have inadequate corpus luteum function. (From ref. 12.)



It is clear that the period of lactational amenorrhoea is dependent on the suckling input (2,12). While this is maintained, ovarian activity is suppressed. However, the amount of suckling input is very difficult to define, since suckling patterns vary considerably among different societies. In our own study group of over 70 women in Edinburgh, a suckling frequency of more than five times and more than 65 min (minimum, 10 min per feed) each day is sufficient to maintain complete suppression of ovarian activity (7,13). Any decrease below these limits in *either* suckling frequency or duration results in the resumption of follicular development. A longitudinal study in Denmark also suggests that suckling five times each day is the minimum required to protect against pregnancy in developed countries (14). While further studies of women in Edinburgh have confirmed our findings, similar longitudinal studies in other societies must be undertaken to determine the parameters necessary for maintenance of lactational amenorrhoea. It is probable, with a frequency which is considerably greater than the Edinburgh norm, that duration of each individual suckling episode may lose importance in maintaining amenorrhoea.

It is well known that suckling causes the release of prolactin, that the amount of prolactin released appears to decline with time postpartum (1,2), and that there is a close correlation between basal plasma levels of prolactin and both suckling frequency (2–4) and duration (8,9). Although during the period of lactational amenorrhoea both suckling frequency and duration are maintained (9,10), there is a gradual decline in basal levels of prolactin. However, basal levels remain above the upper limit of those in the menstrual cycle (Fig. 3). More recently we have shown that the amount of prolactin released during suckling in the afternoon is significantly greater than in the morning (15) (Fig. 4). Since both the feed volume and duration of suckling were the same, this suggests that there may be a difference in sensitivity of the hypothalamic releasing mechanism for prolactin in response to suckling. A diurnal variation in prolactin secretion is well recognized in non-lactating women (16). This may be of considerable significance, since amenorrhoea appears to be prolonged if night feeds are maintained (12).

In spite of the close correlation between suckling-induced hyperprolactinaemia and lactational amenorrhoea (8,17,18) the mechanism by which suppression of ovarian activity occurs remains uncertain. Normal follicular development depends on both FSH and LH. Previous studies during lactational amenorrhoea have demonstrated that injection of GnRH results in a normal increase in both LH and FSH by 30 to 40 days postpartum (see ref. 1), indicating that there is sufficient gonadotrophin reserve in the pituitary for normal gonadotrophin secretion. Indeed, in breastfeeding, as in non-breastfeeding women, plasma levels of FSH recover rapidly and are within the normal menstrual cycle range within 20 to 30 days postpartum (3–6). Thus, it is improbable that a lack of FSH can be responsible for the failure of ovarian development.

On the other hand, basal levels of LH do appear to be reduced in the majority of women during lactational amenorrhoea (2,6,19). However, in the normal menstrual cycle, LH is released in a pulsatile manner (20–22) as a result of a pulsatile release of GnRH from the hypothalamus, and the frequency of pulses appears to

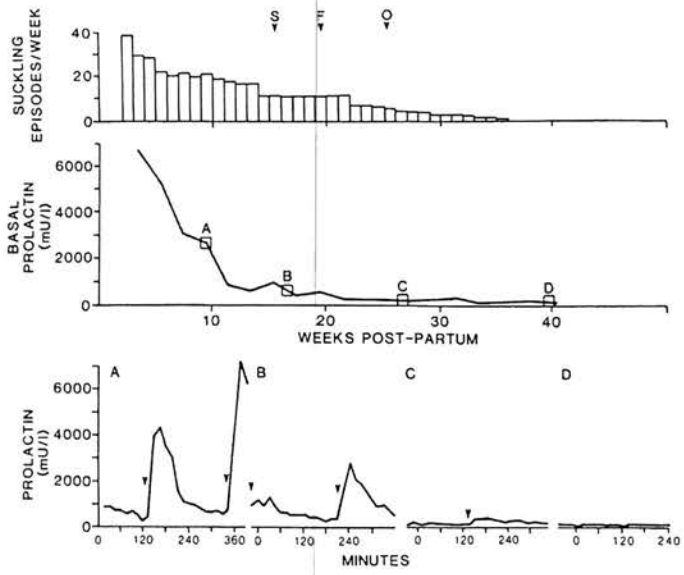


FIG. 4. Changes in suckling frequency and basal plasma levels of prolactin with time postpartum and the prolactin response to suckling during this period. The time of introduction of supplements *(S)*, onset of follicular development *(F)* and of ovulation *(O)* are indicated. At 10 *(A)*, 17 *(B)*, 27 *(C)*, and 40 *(D)* weeks, blood samples were collected at 15-min intervals for 6½ hr. The onset of suckling is indicated *(V)*. Note that when suckling occurred, the prolactin response was greater in the afternoon than in the morning. (From ref. 15.)

be of critical importance for follicle development (23,24). Previous reports have suggested that there is a reduction in or absence of pulsatile LH secretion in women with lactational amenorrhoea (25–28). We have recently confirmed that there is a suppression of the basal levels of LH, which is related to low-frequency, low-amplitude pulses of LH (19). However, this was found in only 70% of the observation periods during lactational amenorrhoea. In the remaining 30% of periods, basal levels and pulse amplitude and frequency of LH were similar to those in the follicular phase of the subsequent normal menstrual cycles in these women (19). This pulsatile secretion was also associated with an increase in urinary levels of oestrogen, indicating follicular development, although the levels of oestrogen did not rise into the range seen in the early follicular phase of the cycle (A. Glasier and A. S. McNeilly, *unpublished observations*), indicating that follicular development was not sustained as in the normal cycle (29). It has been shown previously that breastfeeding women are more sensitive to the negative feedback effects of



oestrogen than are non-lactating women (30,31) and fail to show the normal positive feedback response (Fig. 5).

It should also be remembered that if the hypothalamic GnRH neurons were not under any inhibition, then LH levels in breastfeeding women who have very low levels of oestrogen should be in the postmenopausal range. Clearly, this is not the case, suggesting that there is a reduced ability of the hypothalamus to release GnRH. Thus, although apparently normal pulsatile LH secretion occurs 30% of the time during lactational amenorrhoea and can stimulate ovarian oestrogen secretion, it is probable that this low level of oestrogen is sufficient to switch off the reduced GnRH release at the hypothalamus, preventing further LH release and terminating follicular development (19,29; Fig. 6).

The question that arises is whether the neural suckling stimulus alone is responsible for the suppression of GnRH release or whether it operates in combination with the raised levels of prolactin. Since prolactin and suckling are so closely related, this question remains unresolved.

In amenorrhoeic patients presenting with a prolactin-secreting pituitary tumour, resumption of menstruation and pregnancy can be induced by normalization of prolactin, either by surgical removal of the tumour or treatment with pharmacological dopamine receptor agonists such as bromocriptine (1,2). This suggests that high levels of prolactin, as seen in lactation, could be responsible for the suppression

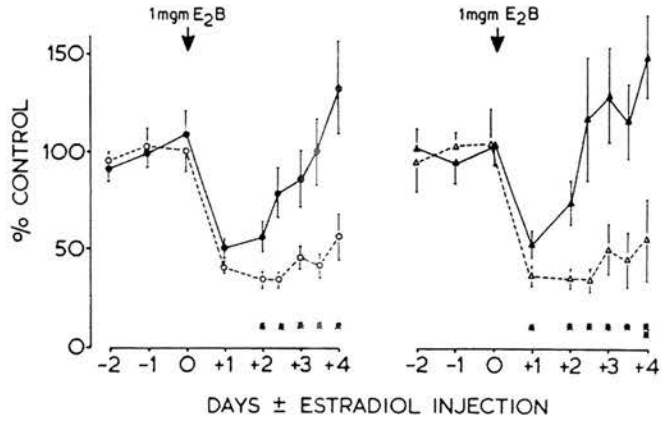


FIG. 5. The concentration of FSH and LH in plasma of seven breastfeeding (○–○) and seven non-breastfeeding (●–●) women before and after the injection of 1 mg oestradiol benzoate ($E_2B$) at 100 days postpartum. Results are expressed as a percentage of the mean basal values before injection. In non-lactating, non-breastfeeding women, all of whom had resumed normal menstrual cycles, $E_2B$ induced negative and positive release of LH and FSH. In contrast, breastfeeding women failed to show a positive feedback response but had a significantly enhanced negative feedback response. (From refs. 30 and 50.)

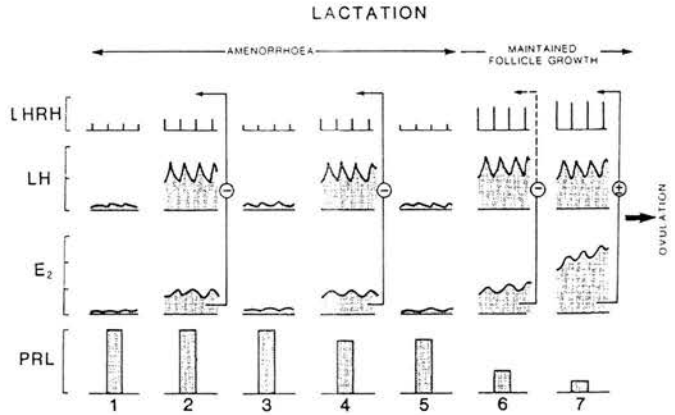


**FIG. 6.** Diagrammatic representation of the control of gonadotrophin secretion and interaction with prolactin during lactational amenorrhoea and resumption of follicular growth and ovulation in breastfeeding women. Suckling causes a decrease in hypothalamic capacity to release GnRH, with subsequent reduced pulsatile secretion of LH *(1)* in the face of high prolactin levels. Pulsatile secretion of LH occurs 30% of the time in lactational amenorrhoea and initiates follicular development with an increase in oestrogen secretion *(2)*. However, because of the increase in sensitivity to the negative feedback effects of this oestrogen, probably because of the reduced hypothalamic capacity to release GnRH, pulsatile LH secretion is switched off *(2)* and further LH secretion is inhibited *(3)*. This process continues until the suckling stimulus and prolactin levels decrease *(5,6)*, at which time hypothalamic capacity returns to normal with normal negative/positive feedback action of oestrogen, allowing maintained pulsatile LH secretion and sustained follicular growth, ovulation, and luteal function (7). (From ref. 50.)

of GnRH and LH secretion, since the pattern of LH secretion is often similar to that in hyperprolactinaemic patients (25,32). However, the aetiology of pituitary tumours remains unknown (33), so the relevance of these observations remains questionable.

Similarly, it has been suggested that prolactin might act directly on the hypothalamus to increase turnover of dopamine, the prolactin-inhibiting factor (34). Such a short-loop feedback system, by which prolactin controls its own secretion, appears to operate in primates as well as in rodents (34). Since an increase in dopamine will also suppress the secretion of LH in women, it is possible that the raised levels of prolactin induced by suckling might suppress GnRH and LH secretion by an increase in dopamine. However, recent studies in the rat (35,36) have shown that lactation is associated with a significant reduction in basal hypothalamic dopamine turnover, casting considerable doubt on the theory of dopamine-mediated suppression of GnRH secretion.

Thus, it may be that the raised levels of prolactin merely reflect the strength of the suckling stimulus, although how this is relayed through the hypothalamic-



pituitary axis is not yet clear. Clearly, maintenance of the suckling stimulus is all important. In our own studies, suckling frequency and duration are both important, although duration may become so only when frequency is low. This remains to be determined. Similarly, the pattern of suckling during each suckling episode may also be important in determining how effective suckling will be in releasing prolactin and suppressing gonadotrophin release. This has yet to be investigated and may prove to be of considerable importance, since it has recently been shown that the suckling rate will vary depending on milk flow (37). Changes in milk flow and suckling patterns in women with lower than normal milk outputs have yet to be studied and may be of considerable importance in determining the effectiveness of suckling in suppressing ovarian activity.

### Resumption of Ovarian Activity

At some stage during lactational amenorrhoea, follicle growth occurs and is sustained. Cross-sectional studies have not been able to define any specific change which can explain the transition from a failure to a maintenance of follicular growth. However, in our own longitudinal studies it is now clear that resumption of follicular development is associated with a decrease in the frequency and/or the duration of the suckling stimulus (8,10). This is most dramatically caused in some women by the introduction to the baby of supplementary food (8) which, in about half of the women we have studied, resulted in a significant decrease in suckling duration without an immediate change in suckling frequency (8; Fig. 7). This decrease in suckling input resulted in a significant decrease in plasma levels of prolactin (8,38) but no change in plasma levels of LH or FSH (6,9,19). The resumption of ovarian activity was also independent of time postpartum (and therefore of infants' age), occurring over a range between 14 and 82 weeks postpartum, and of maternal body weight (8,9,39).

Whether the introduction of supplementary food to the baby resulted in resumption of follicular development depended on the impact on suckling behaviour (8). If suckling declined rapidly, then not only did follicular development occur but ovulation also resumed (Fig. 7). In contrast, if supplements caused only a small reduction in suckling, then prolactin levels fell more slowly, and follicular development and ovulation were delayed for a further variable time (8,10; Fig. 7).

### Ovulation and Pregnancy During Amenorrhoea

There is some dispute about the frequency of ovulation in the cycle before the end of lactational amenorrhoea, the estimates varying from 14% (40), 23% (41), and 33% (8) to 75% (42). These different estimates may be partly explained by the different methods used to assess ovulation (12) but are more likely due to the different suckling patterns of the populations studied. It has been shown that the longer the first menses is delayed during lactation, the more likely is the first cycle to be ovulatory (8,42). In addition, our own studies suggest that continuation of night feeds will also delay the onset of ovulation (Fig. 8).

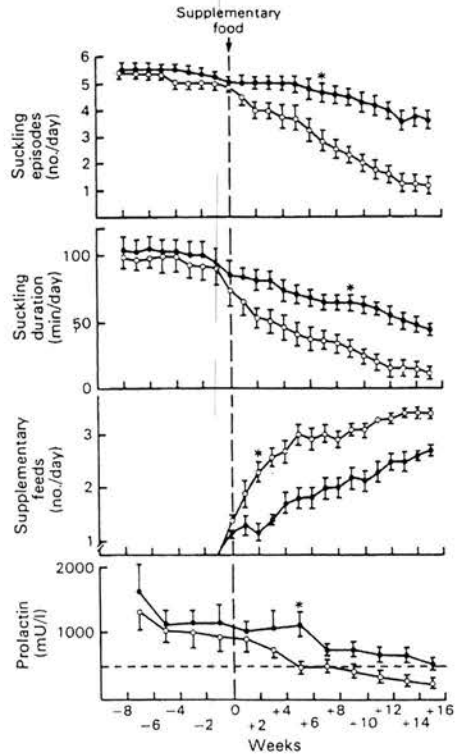


**FIG. 7.** Comparison of infant feeding patterns and basal prolactin between (○) mothers ovulating within 16 weeks ($n = 14$) and (●) mothers suppressing ovulation ($n = 13$) after introduction of supplementary food. Values are mean ± SEM. The broken line indicates the upper limit of prolactin for non-pregnant women. *$P<0.01$ from marked time point onwards. (From ref. 8.)

Resumption of ovulation after prolonged lactational amenorrhoea may result in conception rates of up to 10% (43). To our knowledge, the changes in hormonal status and suckling parameters have been documented in only three cases (4,13). In all of these, ovulation and pregnancy occurred after follicular development resumed when suckling was dramatically reduced (4,13). Thus, much more effort should be directed to documenting the changes in suckling patterns around the time of any conception occurring during lactational amenorrhoea, since there is no



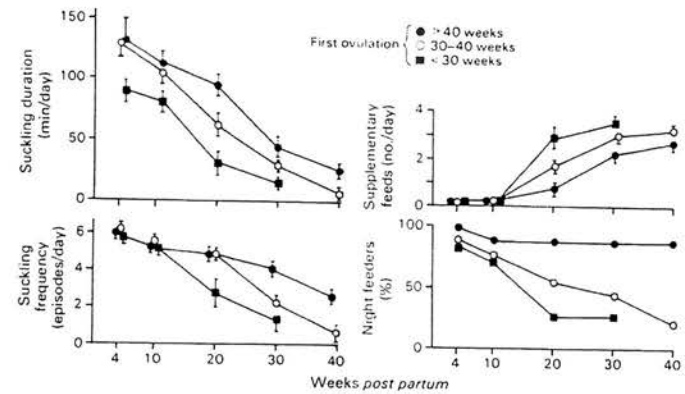


**FIG. 8.** Comparison between infant feeding patterns in breastfeeding women ovulating before 30 weeks ($n = 7$), between 30 and 40 ($n = 9$), and after 40 weeks ($n = 9$) postpartum. Values are mean ± SEM. Note that women in whom ovulation is delayed maintain both suckling frequency and duration, and over 90% feed at night time. This maintenance of suckling was associated with a slower introduction of supplementary feeds. (From ref. 12.)

recurrence of menstruation to warn of the impending return of fertility. This can be done only by longitudinal tracking of breastfeeding women who do not use contraception. Cross-sectional studies will not provide an answer.

## MENSTRUATION DURING LACTATION

It is now clearly established that corpus luteum function in first complete menstrual cycles in breastfeeding women is associated with inadequate progesterone secretion (7,9,17,18,44; Figs. 3 and 9). Indeed, in a total of 49 menstrual cycles occurring during lactation we found that pregnanediol levels in the luteal phase were within normal limits in only 13 (27%) cycles, the remainder of the luteal phases being deficient (31%) or absent (42%). The proportion of normal luteal phases remained low during the first cycles after lactation (6/23) but rose to 24/31 in subsequent cycles (7). Thus, the continuation of the suckling stimulus and the associated marginal hyperprolactinaemia appear to influence luteal function after ovulation. A similar inadequacy of luteal function in first cycles postpartum in non-breastfeeding mothers has also been reported (7,45) and did not appear to be related to excessive plasma levels of prolactin.

Nevertheless, our own studies suggest that maintenance of suckling, once ovulatory menstrual cycles have resumed, leads to a prolonged series of inadequate luteal phases (7,13; Fig. 3). In several instances, the maintenance of night feeds with only token suckling during the day appeared sufficient to reduce luteal function (13).

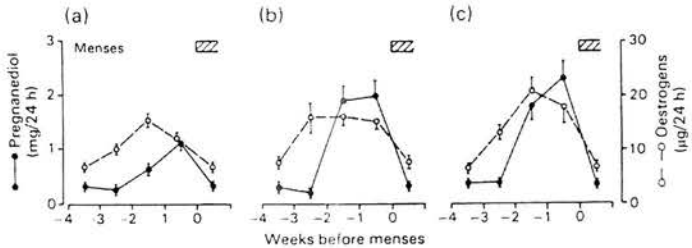


**FIG. 9.** Excretion of urinary total oestrogen and pregnanediol in menstrual cycles *(a)* during lactation ($n = 54$), *(b)* after lactation ($n = 30$), and in non-pregnant controls ($n = 27$). Note that although the urinary pregnanediol is significantly reduced during lactation, indicating inadequate corpus luteum function, oestrogen levels were not significantly different. (From ref. 7.)

In non-breastfeeding women it has been suggested that inadequate corpus luteum function results from a reduction in the FSH-LH ratio around the time of menses, i.e., 10 to 15 days before ovulation (46). Plasma levels of FSH are always at the upper limit of normal (3–6). However, basal plasma levels of LH appeared to be marginally lower than normal during inadequate luteal phases (6), although the pulsatile secretion of LH appeared to be normal (19).

More recently we have measured the changes in urinary steroids and gonadotrophins in early morning urine specimens collected daily during lactational amenorrhoea, through a series of inadequate luteal phases during breastfeeding, until the return of normal menstrual cycles (A. Glasier and A. S. McNeilly, *unpublished observations*). In all 8 cases involving 19 inadequate luteal phases, the increase in oestrogens in the follicular phase was similar regardless of subsequent luteal function (Fig. 10), suggesting that follicular development was normal. In contrast, there was a progressive increase in the amount of pregnanediol excreted during the luteal phase in consecutive menstrual cycles, showing a gradual improvement in corpus luteum function with successive cycles. This was associated with a progressive decline in suckling, until complete weaning occurred and normal luteal function was achieved. This progressive improvement was also associated with a progressive increase in the amount of LH released during the midcycle preovulatory surge (Fig. 10).

Thus, it would appear that suckling can in some way disrupt the normal generation of the preovulatory surge and result in a failure to discharge normal amounts of LH around the time of the final maturation of the preovulatory follicle and may be the cause of the subsequent inadequate corpus luteum function. If this were the case, then it could be envisaged that the duration of menstrual cycles with inadequate corpus luteum function is dependent on the duration of concomitant suckling activity, perhaps in particular night-time feeds. We have previously shown that prolactin response to suckling is greater in the afternoon than the morning (15).



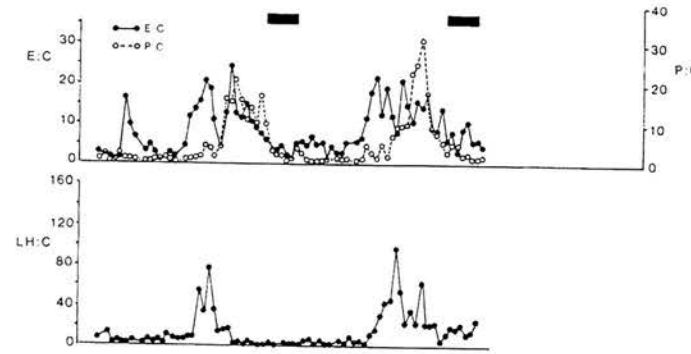


**FIG. 10.** Changes in urinary oestrogen *(E:C)*, pregnanediol *(P:C)*, and LH *(LH:C)* in early morning urine specimens collected daily throughout consecutive menstrual cycles over the transition from lactational amenorrhoea to menstruation. Results are corrected and reported in terms of units per gram of creatinine. Menstruation is indicated by the solid bar. Note that whereas there is little difference in oestrogen secretion before each rise in pregnanediol, total pregnanediol excretion in the second cycle is greater than in the first cycle. Similarly, there is a significant increase in the amount of LH released around midcycle. (A. Glasier and A. S. McNeilly, *unpublished observations.*)

More recently it has been established that in the normal menstrual cycle the start of the preovulatory surge of LH occurs at night in the majority of women (47,48). Thus, it is tempting to speculate that night-time suckling is more likely to suppress the generation of a normal preovulatory LH surge, thus leading to the formation of an inadequate corpus luteum. While the suckling stimulus is maintained, inadequate luteal function will occur. Clearly, this will require considerable further investigation, since the causes of inadequate corpus luteum function in the menstrual cycle are almost certainly a complex of endocrine changes. It also remains possible that the high levels of prolactin might directly inhibit follicular development at the ovarian follicle, but there is no clear evidence to support this in women (49,50).

## CONCLUSIONS

Our studies conclusively confirm that breastfeeding, even in an industrialized, well-nourished population, will suppress fertility for a considerable period of time (up to 75 weeks). Resumption of ovarian follicular development and ovulation occurs only when suckling frequency decreases below five feeds each day, with a total daily suckling duration of less than 65 min/day. Ovulation will resume if total suckling activity is below this level, even if no supplementary food is being given and the baby is receiving breast milk as its sole source of nutrition.

The resumption of follicular development and ovulation occurs when there is a significant decrease in suckling input below that indicated above. This can be

precipitated by introduction of supplementary food, presumably by reducing the baby's dependence on breast milk; but resumption of ovarian activity is not dependent on age of baby or maternal body weight.

First menstrual cycles are normally associated with inadequate luteal function, which tends to continue if suckling is maintained. Rapid reduction in suckling, or weaning, especially if occurring after prolonged lactation, can result in ovulation with normal luteal function, with the potential to carry a pregnancy if conception occurs. This appears to explain the occurrence of pregnancies during lactational amenorrhoea in the cases where adequate data is available.

Reduction in the pulsatile secretion of LH appears to be mainly responsible for the absence of follicular development during lactational amenorrhoea. Whereas pulsatile LH secretion may occur between 20 and 30% of the time and stimulate limited follicular development, suckling appears to reduce the ability of the hypothalamus to maintain pulsatile GnRH and hence LH secretion, and follicular development ceases.

Inadequate corpus luteum function appears to be related to plasma levels of prolactin above normal and to a reduced midcycle surge of LH. Suckling may directly interfere with the generation of a normal preovulatory LH surge, whereas prolactin may interfere directly at the ovarian level to suppress ovarian response to gonadotrophins. However, the mechanisms whereby the suckling stimulus decreases GnRH output from the hypothalamus remain unknown. It is clear that the maintenance of infertility during breastfeeding is directly dependent on the strength of the suckling stimulus. Anything that undermines or reduces this stimulus will result in a resumption of ovarian activity with a variable return in fertility.

## ACKNOWLEDGEMENTS

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## COMMENTARY

*During the course of our discussion at the workshop, Dr. McNeilly was asked to respond to certain points, and he has therefore contributed the following extra paragraphs.*

*Editor*

A. S. McNeilly

### Methods of Assessing Resumption of Ovarian Activity

Clearly, the only satisfactory method of assessing resumption of ovarian activity is a measure of the increase in oestrogen secretion. The increase in progesterone or pregnanediol, being products of the corpus luteum, occurs after ovulation, by which time conception and thus pregnancy could have occurred. It is possible that a measure of electrolyte changes using a dipstick for saliva or breast milk might be used, as there are indications of significant changes in electrolytes in the mid-follicular phase of the menstrual cycle (1).



More directly, a simple method for the measurement of oestrogen needs to be developed. In terms of chemical endpoints, a dipstick method could be developed which would measure an increase in oestrogens in blood, urine, or saliva. The latter two are the only practical body fluids for such a test. A simpler and equally appropriate method is the measurement of cervical mucus output as in the Billings method (2). The increase in mucus production is dependent on increasing amounts of oestrogen, and thus any increase in mucus in a breastfeeding women, who during lactational amenorrhoea often has very low oestrogen levels, would be potentially an excellent marker for the resumption of ovarian activity.

### Comparative Aspects of the Role of Prolactin in the Suppression of Ovarian Activity

This is an immensely complex subject which has been reviewed recently (3). Studies in rats may be very misleading, in particular in terms of effects of prolactin and corpus luteum function, since no function will occur in the absence of high levels of prolactin, which in a woman would be indicative of pathological hyperprolactinaemia and amenorrhoea. Similarly, increases in prolactin induce an increase in dopamine turnover in the hypothalamus of the rat, mouse, and hamster. In the rat this is associated with a decrease in gonadotrophin secretion, whereas in mice and hamsters gonadotrophin secretion is enhanced. Finally, dairy cows, which are milked twice daily, return to oestrous between 30 and 90 days postpartum. If they are suckled by four calves, oestrous onset is delayed up to 300 or more days. In both cases, however, plasma levels of prolactin are the same. Thus, it is very difficult to rationalize the variable effects of prolactin to a single mechanism for the suppression of ovarian activity.

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*C. Robyn:* Is the frequency as important as the duration of suckling in maintaining the lactational hyperprolactinaemia? Could animal data contribute to answer this question?

*A. S. McNeilly:* The principal suppressor of gonadotrophin secretion, apparently through suppression of the ability of the hypothalamus to generate and maintain pulsatile secretion of GnRH, is the suckling frequency. It appears that when suckling frequency is high, 10 to 20 times per day, then duration of each suckling episode is not very critical. However, when suckling frequencies decline to levels normal in the Western world, i.e., five to six times per day, then duration does become of importance. It is clear from our data that a decline in suckling duration alone is enough to trigger resumption of ovarian activity in the absence of a change in suckling frequency.

I do not believe animal studies will help unravel the relative importance of frequency and duration any better than more studies in different human cultural situations.

*C. Robyn:* Auditory, olfactory, and visual exteroceptive stimuli contribute to increased serum levels of prolactin in animals. I am not aware of data on the influences of these

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# FSH AND THE CONTROL OF FOLLICULAR GROWTH

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**Summary**—During 70 days or so from the time of recruitment until just before the beginning of the cycle during which a follicle is destined to ovulate, folliculogenesis is a continuous process dependent on gonadotrophins but independent of the fluctuations in their concentrations occurring during this time. For follicle growth to continue beyond the 2–4 cell antral stage FSH concentrations must rise above a certain threshold level at the correct time. Once threshold levels are exceeded a single follicle becomes dominant suppressing FSH concentrations to subthreshold values. The period during which FSH concentrations are above threshold can be imagined as a gate through which a follicle must pass if it is to ovulate.

## INTRODUCTION

In the human female 99% of oocytes formed during fetal life undergo atresia or degeneration [1] and normally only one preovulatory follicle develops to the point of ovulation. In this paper we shall consider the role of gonadotrophins and in particular of FSH in folliculogenesis and in the process of follicle selection and dominance.

## RECRUITMENT

The ovarian follicle destined to ovulate is drawn from a pool of non-growing primordial follicles, each consisting of an oocyte, a few granulosa cells and a basement lamina. Within the ovary at any one time 90–95% of all follicles are primordial and only a few are recruited into the growing pool. The cohort of growing follicles undergoes a process of development and differentiation which takes about 85 days and spans three ovarian cycles [2]. During this process normally only one follicle will eventually ovulate, the rest undergo atresia at various stages of development.

## MECHANISMS OF RECRUITMENT

Mechanisms involved in the process of recruitment are poorly understood, but appear to be independent of pituitary control and probably depend on ovarian paracrine mechanisms [3]. The number of primordial follicles recruited into the growing pool is not constant but varies with age, being greatest in early life [4] and decreasing progressively with advancing years. In addition the fraction of primordial follicles recruited is probably a function of the actual size of the total pool available which appears to be affected by testosterone [5] and may be influenced by other factors such as nutrition, activity of the thymus gland and opioid peptides.

## INTERMEDIATE FOLLICULAR DEVELOPMENT

Over the next few weeks the recruited follicles undergo development and differentiation. The number of granulosa cells increases; the oocyte becomes fully grown and a zona pellucida develops; theca cells align outside the basement lamina and the follicle acquires an independent blood supply [6]. Only a fraction of the total number of follicles that started the growth sequence reach the stage of becoming potential ovulatory follicles, i.e. follicles capable of undergoing maturation to the point of ovulation. At the start of the menstrual cycle there are probably

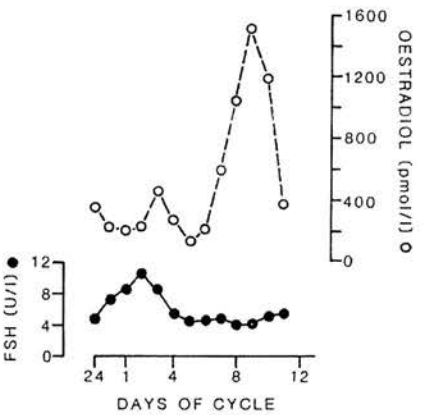


Fig. 1. Intercycle FSH rise ●—● stimulating follicle growth and oestradiol production ○—○ in a spontaneous normal menstrual cycle.

Proceedings of the XIII Meeting of the International Study Group for Steroid Hormones (Rome, Italy, 30 November–2 December 1987).

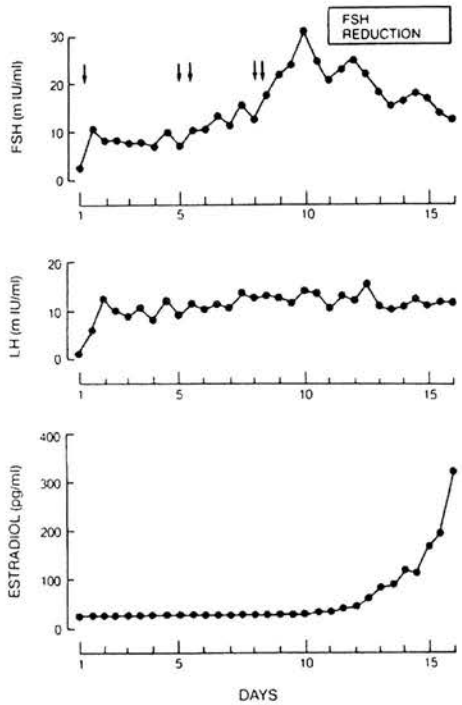


Fig. 2. From Zeleznik A. J. and Kubik C. J. (1986) *Endocrinology* **119** 2025–2032. Plasma gonadotropin and oestradiol concentrations in a cynomolgus monkey infused with hFSH and hLH at a frequency of 1 pulse/h. The first arrow indicates the initiation of hFSH and hLH infusion. The subsequent double arrows indicate a doubling of the amount of FSH given per pulse. After the initial rise in serum oestradiol concentration, the amount of FSH was reduced by 12.5%/day.

only about 20 or so precursor follicles [1] 2–4 mm in diameter capable of further development, a process which depends on the appropriate gonadotrophin stimulation.

As the previous corpus lutuem regresses, FSH secretion increases [7] (Fig. 1). This rise in FSH is thought to propel suitably responsive precursor follicles into the final phase of their growth cycle. Follicles which reach this stage of development at any other time will not receive adequate LH stimulation and will become atretic [8]. It may be that by increasing the amount of FSH available or prolonging the duration of the late luteal phase rise more follicles would be available for development in the follicular phase of the next cycle. For follicular development to occur at all, gonadotrophin concentration must be above a certain threshold requirement. Treating women with hypogonadotrophic hypogonadism, Brown 1978 [9] showed that ovaries remained unresponsive to subthreshold levels of gonadotrophins even if the same dose was continued indefinitely. The threshold varies between individuals by as much—in the case of exogenous gonadotrophin therapy—as a factor of 10. A stepwise increase in the dose of gonadotrophins will identify the threshold requirement and when this is attained follicular development begins. In a given individual the difference between a subthreshold dose and a dose sufficient to stimulate follicular development may be as little as 20%. While early follicular phase rises in FSH concentrations are only small, the increase is nevertheless enough to initiate follicular development beyond 4 mm. If this early follicular phase rise is inhibited by oestradiol injection or by the injection of follicular fluid, follicular development is suppressed [10].

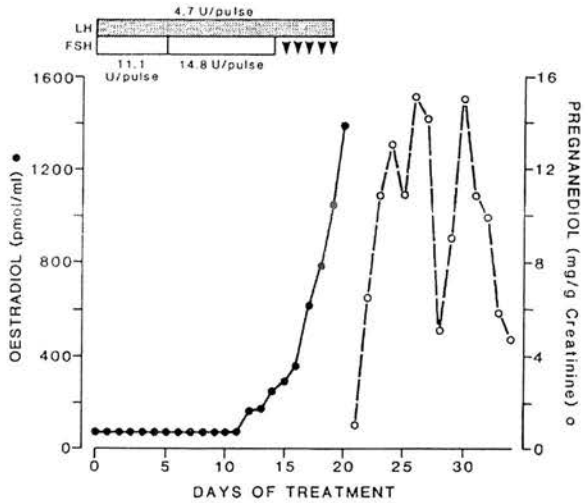


Fig. 3. Plasma oestradiol and urinary pregnanediol concentrations in a woman with hypogonadotrophic hypogonadism treated with LH 4.7 U/pulse and a dose of FSH increased by 30% after 5 days. Following the initial oestradiol response FSH was reduced ▼ by 10%/day—follicular development continued to ovulation.

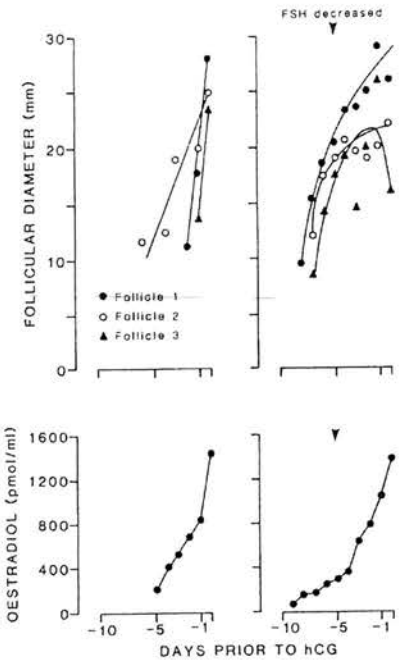


Fig. 4. Growth of the three largest follicles in a woman with hypogonadotrophic hypogonadism. Treated in the first cycle with FSH concentrations maintained above threshold levels all three follicles continued to grow. In the second cycle the amount of FSH per pulse was reduced by 10%/day from the time of the initial rise in oestradiol ●—●. Only the largest follicle ● continued to increase in diameter, the second ○ and third ▲ largest appeared to undergo atresia.

There is good evidence from the work of Goodman [11] in the rhesus monkey, and Nilsson in the human [12], that follicular development at this stage is subject to critical phases. Destruction of either the dominant follicle or the corpus luteum results in a delay of about 14 days before a second follicle reaches the same stage of development. This suggests that at the time of ablation the follicle destined to ovulate has already been irrevocably selected and no other follicle is capable of substituting for it. The dominant follicle inhibits growth of both new follicles and less mature follicles and the next follicle to ovulate is the product of a new cohort of follicles which develop subsequently.

## SELECTION

Developing follicles acquire FSH receptors during the early stages of differentiation. Binding of FSH stimulates the induction of aromatase systems enabling the aromatisation of androgens, produced by theca cells under the influence of LH, to oestrogens. In response to stimulation by FSH and oestradiol the precursor follicles eventually also acquire LH receptors. The follicle which most rapidly acquires aromatase activity and LH receptors probably becomes the dominant follicle [8].

In natural cycles normally only one follicle is destined to ovulate. Once a follicle has acquired dominance its presence appears to inhibit the growth of less mature follicles.

Zeleznik and Kubik [13] 1986 recently reported the results of a study in macaque monkeys demonstrating that after stimulation by elevated FSH concentrations, follicles can continue to mature in the presence of FSH concentrations which are unable to support the growth of less mature follicles. Animals were treated with a GnRH antagonist to block endogenous gonadotrophin secretion. Follicular development was then initiated with a constant dose of LH and a dose of FSH which was increased every 3–4 days until the initiation of oestrogen secretion, i.e. until the threshold level for follicular growth was reached. A progressive reduction in FSH dose over the subsequent 5 days to concentrations below the threshold dose was accompanied by continued preovulatory follicular growth (Fig. 2).

In Edinburgh, we are carrying out a similar study in women with hypogonadotrophic hypogonadism. Follicular development is initiated with a constant dose of LH given subcutaneously in a pulsatile manner. The dose of FSH, also given in a pulsatile manner, is increased every 5 days by 30% until the threshold level—determined by increasing oestradiol secretion and ultrasound evidence of follicular growth—is reached. FSH administration is then either continued at the threshold dose or decreased by 10% each day (Fig. 3). In the women who have so far completed treatment, reducing the dose of FSH below threshold levels results in a reduction in follicular diameter in the majority of developing follicles (Fig. 4).

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# 178TH MEETING
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## 159 BOTH LH & FSH ARE REQUIRED FOR THE DEVELOPMENT OF THE NORMAL FOLLICLE

A.F.Glasier, E.J.Wickings, M.W. Rodger, S.G.Hillier and D.T.Baird; Department of Obstetrics & Gynaecology, University of Edinburgh, Centre for Reproductive Biology, 37 Chalmers Street, Edinburgh EH3 9EW

The current hypothesis for selection and growth of the preovulatory follicle involves activation with FSH; increasing oestrogen secretion dependent on the conversion of thecal androgen stimulated by LH; and subsequent suppression of pituitary FSH by rising levels of oestrogen. This implies that the dominant follicle must become increasingly sensitive to FSH. We have tested these hypotheses relating to follicle growth in two women with hypogonadotrophic hypogonadism. In experiment 1 follicular growth was induced by either Metrodin (FSH) or Pergonal (FSH and LH) the dose being increased by 30% every 5 days. In the second experiment when the threshold was reached (plasma $E_2$ concentration $\geq$300 pmol/l) the dose of FSH was reduced by 10% each day. 5000 units of hCG were injected when the $E_2$ concentration reached $\geq$1000 pmol/l (day 0). In experiment 1 on day 0 the number of large antral follicles was much greater in the cycles treated with FSH alone than with LH and FSH(9 & 12 vs 3 & 2) and the plasma $E_2$ / follicle was abnormally low (268 & 92 vs 547 & 553 pmol/l). In experiment 2 when the dose of FSH was reduced there were fewer large antral follicles than when it was maintained above the threshold level (2 & 2 vs 5 & 5). We conclude that (1) both FSH and LH are required for normal secretion of $E_2$ by the preovulatory follicle confirming the two cell hypothesis (2) once selected the preovulatory follicle can continue growing in the presence of subthreshold levels of FSH..

# 6 Lactation and the Return of Ovulation

Alan S. McNeilly, P.W. Howie and Anna Glasier

Worldwide, breast feeding is associated with a reduction in fertility which is of major demographic importance (Rosa, 1975). However, there is considerable variation in the length of the period during which breast feeding suppresses fertility, both within and between societies. Recent studies have shown that it is the suckling stimulus itself which suppresses ovarian activity and the reason for the variability in the infertile period and is due almost entirely to variations in the strength of the suckling stimulus.

In a noncontracepting breast-feeding woman, the interbirth interval (Figure 6.1) can be divided into four main components: (1) the recovery of the hypothalamo-pituitary (gonadotrophin) axis from the suppressive effects of placental steroids during pregnancy: in a nonbreast-feeding woman this lasts from twenty to 30 days; (2) the period of lactational amenorrhoea; (3) a period when ovulation returns which may or may not be followed (a) by adequate corpus luteum function capable of maintaining a pregnancy, or (b) by menstruation; and, (4) pregnancy. In a nonbreast-feeding woman, ovulation and menses returns by four to ten weeks postpartum (Howie and McNeilly, 1982; Gross and Eastman, 1985; Poindexter, Ritter and Besch, 1983). In contrast, breast feeding-induced amenorrhoea may last from two to three months in an early weaning population to three to four years in populations practising late weaning and frequent nursing (Rosa, 1975; Howie and McNeilly, 1982).

## LACTATIONAL AMENORRHOEA

### Recovery from pregnancy

During pregnancy, the high concentrations of placental steroids suppress the secretion of both gonadotrophins, luteinizing hormone





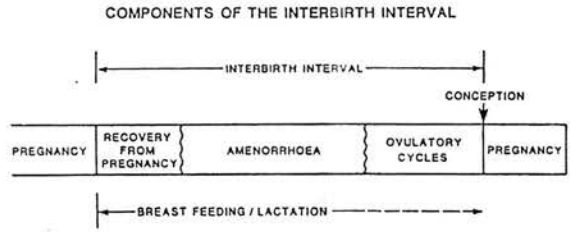


*Figure* 6.1 Components of the interbirth interval in breast-feeding women.

(LH) and follicle stimulating hormone (FSH) to approximately 1 per cent of normal (McNeilly, 1979), whereas the number and activity of the prolactin secreting cells and the plasma concentration of prolactin is increased (Robyn and Meuris, 1982). After parturition and the removal of placental steroids, plasma levels of prolactin decline and those of FSH and LH increase in the absence of breast feeding and ovarian follicle growth, ovulation and menstruation returns by 30–50 days postpartum. First menstruation is usually preceded by an inadequate (80 per cent) or absent (20 per cent) luteal phase in terms of progesterone secretion from the corpus luteum (McNeilly *et al.*, 1982; Poindexter, Ritter and Besch, 1983). Luteal function improves with subsequent menstrual cycles such that normal luteal function is re-established by 70 to 100 days postpartum. There is, therefore, a finite time after pregnancy, during which the hypothalamo-pituitary ovarian axis must recover from the suppressive effects of pregnancy, even in the absence of breast feeding.

### Suppression of ovarian activity in breast-feeding women

Recent studies in Edinburgh, Denmark, Australia, the USA and Mexico where ovarian activity was assessed by measurement of the plasma or urinary levels of ovarian steroids have confirmed that, during lactational amenorrhoea ovulation rarely occurs Andersen and Schøler, 1982; Brown, Harrison and Smith, 1985; Duchen and McNeilly, 1980; Konner and Worthman, 1980; Howie and McNeilly, 1982; Gross and Eastman, 1985; Rivero *et al.*, 1985; Wood *et al.*, 1985; Figure 6.2). These studies have also shown that follicular

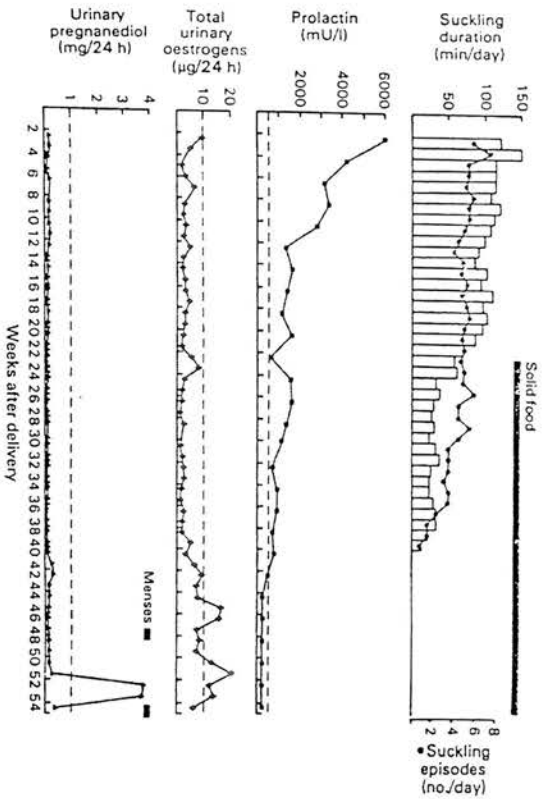


*Figure* 6.2 Changes in urinary total oestrogens and pregnanediol in relation to the suckling frequency and duration and levels of prolactin in a breast-feeding woman. (From Howie and McNeilly, 1982.)

development is also suppressed, measured either as oestrogen levels in plasma or urine (see McNeilly, 1984; McNeilly, Glasier and Howie, 1985) or by ultrasound visualisation of follicles within the ovary (Glasier, McNeilly and Baird, 1986). Ovarian activity may be suppressed completely for almost the total duration of lactational



amenorrhoea (McNeilly, Glasier and Howie, 1985). We have recently observed that, in a proportion of women, follicular development may occur with fluctuating levels of oestrogen being observed for periods of one to two weeks during lactational amenorrhoea. However, these levels of oestrogen do not increase to those seen in the normal preovulatory phase of the menstrual cycle, indicating that follicular development is not normally sustained during lactational amenorrhoea.

The duration of lactational amenorrhoea has now been clearly related to the suckling input. In our own studies of over 100 women in Edinburgh, ovulation was never seen in women with a suckling frequency of more than five times each day and a feeding duration minimum of 10 min per feed. Similar suckling parameters were found in Denmark (Andersen and Scholer, 1982), whilst in women in the USA, amenorrhoea was maintained for up to eighteen months with a suckling duration of 80 min per day, in conjunction with a minimum of six nursing episodes (Stern *et al.*, 1986). These minima may well vary considerably in different societies and must be investigated individually to allow for parameters to be established for each society.

In some societies in which suckling frequency is normally high, the duration of feeds may become less important. For instance, lactational amenorrhoea for up to four years occurs in the !Kung hunter gatherers of the Khalahari in whom suckling frequency is around five bouts per hour but each bout is of very short (2–3 min.) duration (Stern *et al.*, 1986).

### Resumption of ovarian activity

Longitudinal studies have now established that resumption of ovarian activity is associated with a decrease in the frequency and/or duration of the suckling stimulus (Howie *et al.*, 1981, 1982; Andersen and Schøler, 1982; Stern *et al.*, 1986; Delvoye *et al.*, 1980; Figure 6.2). In our Edinburgh study, the introduction of supplementary food to the baby resulted in a significant decrease in suckling duration without an immediate change in suckling frequency in over one-half the women (McNeilly, Howie and Houston, 1980; Howie *et al.*, 1981; Figure 6.2). This resumption of ovarian activity was independent of infants age and thus, time postpartum, and maternal and infant body weight. The effect of supplementary food on ovarian activity depended on its impact on the suckling behaviour of the baby. If this was only slightly affected, then the return of ovarian activity and ovulation was delayed.

while, if suckling declined rapidly, then, not only did follicular development resume, but ovulation also occurred (McNeilly *et al.*, 1983; McNeilly, Glasier and Howie; 1985).

### Ovulation, menstruation and pregnancy during lactation

Previous studies using indirect methods of assessing the return of ovulation (e.g. endometrial biopsy) concluded that ovulation frequently occurred in the cycle before the end of lactational amenorrhoea although estimates varied between 14 and 75 per cent (Howie *et al.*, 1981; Udesky, 1950; Cronin, 1968; Perez *et al.*, 1972). These variations are probably due to the different patterns of suckling in the different societies. The longer the first menses is delayed during lactation, the more likely it is to be preceded by ovulation (Howie and McNeilly, 1982). Although ovulation and menses does resume, conception rates in menstruating breast-feeding women are only about one-third of normal. The probable explanation for this is that a substantial number of menstrual periods are preceded by inadequate luteal function which would not be capable of supporting a pregnancy (McNeilly *et al.*, 1983; Figure 6.3). Pregnancy may occur during lactational amenorrhoea without a preceding menstrual period to warn of the return of fertility. This appears to be a relatively rare occurrence (10 per cent) and is most likely to occur in societies which practise prolonged lactation. In our own studies, three pregnancies occurred without preceding menses and in all three there had been a dramatic reduction in suckling activity just prior to first ovulation (McNeilly *et al.*, 1983; Figure 6.3).

It is possible for women to be amenorrhoeic for a substantial period of time as pregnancy is followed by lactational amenorrhoea, conception occurring before menses, a further pregnancy, etc.

## MECHANISMS CONTROLLING LACTATIONAL INFERTILITY

### Prolactin

A principal effect of suckling is to release prolactin which is essential for the production of milk (McNeilly, 1977; Howie *et al.*, 1980). The duration of lactational amenorrhoea is associated, in many studies



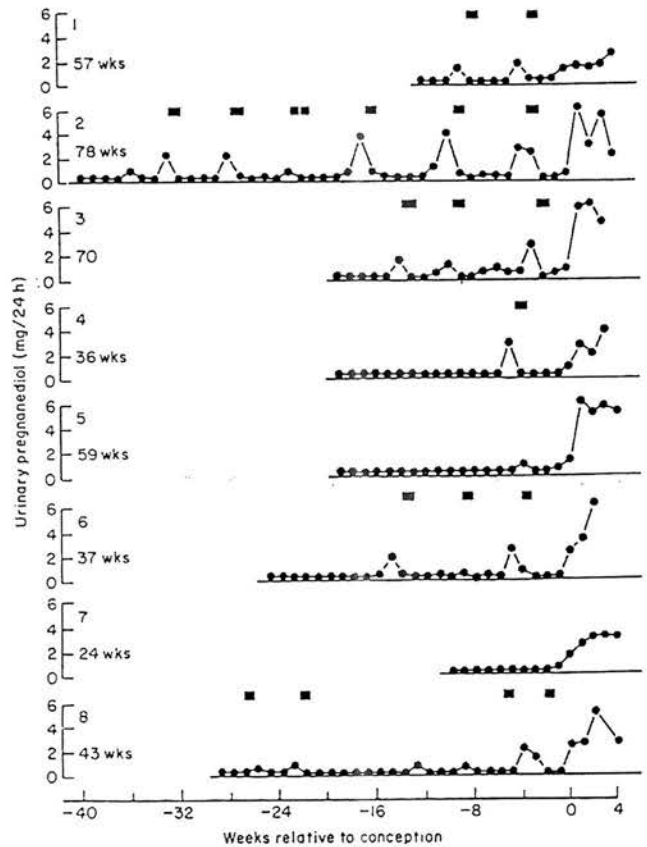


*Figure* 6.3 Changes in urinary levels of pregnanediol (•) as an index of corpus luteum function, and menses (■) prior to conception in seven breast-feeding women. The time of conception in weeks postpartum is also indicated. Note that (1) conception occurred in two women (Nos 5 and 7) before any menstrual period (2) the majority of menstrual periods are preceded by inadequate or absent luteal function. (From McNeilly *et al.*, 1983.)

with raised levels of prolactin (see McNeilly, 1984) which has led to the suggestion that prolactin *per se* may be involved in the suppression of ovarian activity. However, whilst prolactin may be involved, this involvement appears to be minimal and related to the fact that the level of hyperprolactinaemia is directly correlated with suckling activity (McNeilly, Glasier and Howie, 1985).

Ovarian activity can be stimulated during lactational amenorrhoea by treatment with exogenous gonadotrophins (Andreassen and Tyson, 1976; Nakano *et al.*, 1975), in spite of raised levels of prolactin. Thus, lactational infertility is most probably due to a reduction in gonadotrophin secretion.

## Gonadotrophins

During the menstrual cycle, follicle growth is stimulated initially by FSH. Continued follicle growth requires both FSH and LH which is released in a pulsatile manner from the pituitary to stimulate oestradiol secretion (Figure 6.4). The increase in oestradiol reaches a critical level as the preovulatory follicle matures and triggers the mid-cycle surge of LH which causes ovulation and the formation of the corpus luteum (Figure 6.4). The maintenance of follicular development is dependent on the pulsatile secretion of LH which occurs as a result of the pulsatile release of gonadotrophin-releasing hormone (GnRH) from the hypothalamus. In the menstrual cycle, oestradiol appears to increase the frequency of pulsatile GnRH release whereas in the luteal phase progesterone and oestradiol from the corpus luteum suppress the frequency resulting in a reduction in the pulsatile secretion of LH. This decrease appears to be related to an increase in hypothalamic opioid activity which affects the GnRH neurones (Crowley *et al.*, 1985; Lincoln *et al.*, 1985).

During lactation plasma levels of FSH increase within three weeks postpartum and remain within the normal range of the menstrual cycles throughout the postpartum period (see McNeilly, 1979). In contrast to FSH, LH levels only increase to the lower limit of normal by twenty days postpartum and remain suppressed in the majority of women throughout lactational amenorrhoea (Delvoye *et al.*, 1978; Rolland *et al.*, 1975; McNeilly, Howie and Houston, 1980; Glasier, McNeilly and Howie, 1983). These low levels of LH are associated with low amplitude pulses of LH at a frequency similar to or less than that of the luteal phase (Madden *et al.*, 1978; Tyson *et al.*, 1978; Glasier, McNeilly and Howie, 1984). This reduction in LH secretion



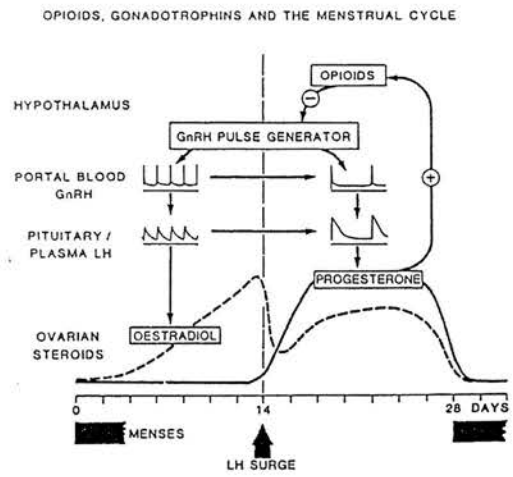


*Figure* 6.4 Schematic diagram of the endocrine changes during the menstrual cycle. The growth of the follicle is initiated by FSH and oestradiol secretion is maintained by the pulsatile secretion of LH. Oestradiol acts at the hypothalamus to maintain or increase the secretion of GnRH which stimulates the pulsatile secretion of LH. The increased levels of oestradiol secreted by the preovulatory follicle triggers the release of the mid-cycle surge of LH which induces ovulation and the formation of the corpus luteum. The secretion of progesterone and oestradiol by the corpus luteum suppresses LH secretion by increasing opioid activity in the hypothalamus which directly suppresses hypothalamic GnRH output. Suckling also appears to stimulate an increase in opiate activity thus suppressing LH output throughout the period of lactational infertility.

indicates that suckling induces a suppression of GnRH release within the hypothalamus. This is also implied by the fact that in breast-feeding women, oestradiol is not capable of inducing a release of LH as seen in the normal menstrual cycle (Baird *et al.*, 1979). Indeed, oestradiol appears to have an increased ability to suppress LH release. Thus, if pulsatile LH release was to resume in lactational amenorrhoea, which can occur up to 30 per cent of the time (Glasier,

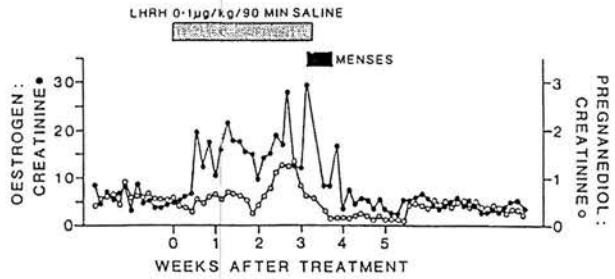


*Figure* 6.5 The induction of ovulation in a breast-feeding woman by the pulsatile infusion of gonadotrophin releasing hormone (GnRH=LHRH) starting at 6 weeks postpartum. Note that ovarian activity as measured by steroid secretion was suppressed before and after GnRH treatment. During treatment follicular development was stimulated and ovulation occurred and a corpus luteum was formed. When the pulsatile infusion of GnRH was stopped, the corpus luteum regressed, pregnanediol and oestrogen levels declined and menstruation occurred. (From Glasier, McNeilly and Baird, 1986.)

McNeilly and Howie, 1984), the subsequent increase in follicular oestradiol secretion would inhibit further GnRH, and hence, LH release and ovarian activity would cease (McNeilly, Glasier and Howie, 1985).

Such a situation would continue until suckling declined to a level whereby GnRH secretion was no longer inhibited. However, if suckling does continue, then the magnitude of the preovulatory LH surge appears to be decreased and this may be the cause of the reduction in luteal function seen in ovulating, menstruating, breast-feeding women (McNeilly, Glasier and Howie, 1985).

We have recently confirmed that it is the inability of the hypothalamus to maintain GnRH output which is responsible for the failure of sustained follicular development and ovulation in breast-feeding women. Follicular development, ovulation and luteal function can be induced in breast-feeding women by the pulsatile administration of GnRH (Glasier, McNeilly and Baird, 1986; Figure 6.5).

The precise mechanism whereby suckling suppresses GnRH output is not clear. Studies in animals suggest that suckling may increase hypothalamic opiate activity which in turn suppresses GnRH release



(Sirinathsinghji and Martini, 1984; Mattioli *et al.*, 1986). Whilst there is no direct evidence for a similar mechanism in women, it is known that heroin will cause a suppression of gonadotrophin and an increase in prolactin secretion similar to that seen in lactation (Pelosi *et al.*, 1974). This preliminary data suggests that suckling-induced release of opioids within the hypothalamus may be the principal mediator of the suppression of LH release during lactation.

## FACTORS INFLUENCING LACTATIONAL AMENORRHOEA

In the absence of contraceptive practices, nutrition has been suggested by some to play a major role in the control of the duration of lactational infertility by a direct effect on the mother (Frisch, 1985). However, there is little evidence to substantiate this direct mechanism whereby the metabolic load placed on the breast-feeding women by the lactation is primarily instrumental in causing the suppression of ovarian activity. Indeed, recent studies suggest that maternal metabolism is reduced during lactation (Illingworth *et al.*, 1986), and different nutritional status does not explain the prolonged duration of lactational amenorrhoea in women in Zaire compared with those in Sweden (Hennart *et al.*, 1985).

In red deer, it was shown that poor nutrition results in a reduction in milk production (Loudon, McNeilly and Milne, 1983; Figure 6.6). This in turn caused an increase in the suckling activity of the young in order to maintain the required milk input per day. This increase in suckling led to a delay in the return of oestrus, i.e. nutrition was having an indirect effect on ovarian activity by altering milk production and, thus, suckling. A similar situation is thought to occur in breast-feeding women (Lunn *et al.*, 1980; Lunn, 1985). A reduction in water intake by the mother might induce a similar change in suckling activity and thus be related to the duration of lactational amenorrhoea.

## BREAST FEEDING AND CONTRACEPTION

Although breast feeding has been shown to suppress fertility on a global scale, the inhibition of fertility is not absolute and the duration varies with individual mothers and infants. Guidelines for suckling

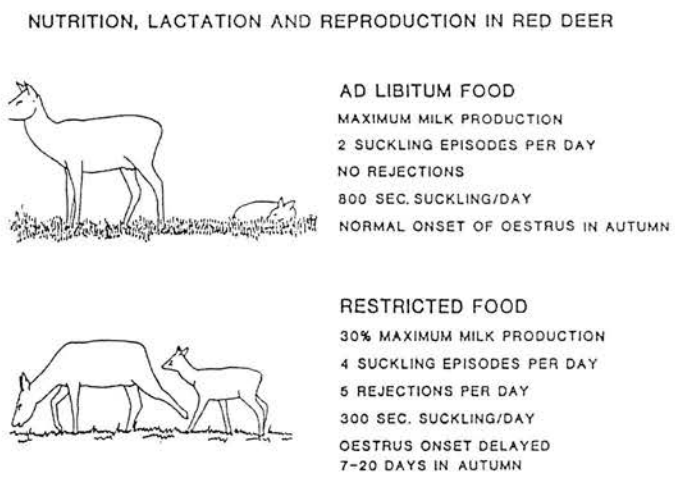


*Figure* 6.6 The effect of nutrition on milk production and oestrous activity in the red deer hind and suckling activity of the calf. Poor nutrition resulted in a reduction in milk production and an increase in the suckling activity of the calf. This caused an increase in maternal levels of prolactin and a delay in the return to oestrus. (From Loudon, McNeilly and Milne, 1983.)

frequencies and durations which will maintain infertility can be determined but these cannot guarantee complete protection. It is necessary, therefore, that breast-feeding women should have contraceptives which will give protection from pregnancy but not adversely affect either milk production or the infant.

**Progestagen only contraception**

The combined oral contraceptive is not recommended since it appears to suppress milk production. As a consequence, most nursing mothers who wish to use an oral contraceptive are advised to choose the progestagen-only pill which does not affect milk production. However, we have recently shown that the frequency of episodes of



vaginal bleeding was substantially greater in breast-feeding women taking the progestagen-only pill compared with breast-feeding women receiving no hormonal contraception (Howie *et al.*, 1986). This increase in vaginal bleeding was not associated with any difference in breast feeding patterns or on the incidence of ovarian activity suggesting a direct effect on the endometrium of the uterus.

A similar, unpredictable, pattern of vaginal bleeding occurs in nonbreast-feeding women (Rice-Wray, Beristain and Cervantes, 1972). Recently, we have shown that the addition of Sulpiride, a dopaminergic antagonist which releases prolactin, substantially improves the efficacy of the progestagen-only contraceptive (Payne *et al.*, 1985). The potential of this contraceptive will soon be explored in breast-feeding women and may have the advantage of not only reducing or abolishing the incidence of vaginal bleeding, but also, by maintaining prolactin, will help maintain lactation.

**GnRH agonist**

In nonlactating women, GnRH agonists delivered either by nasal spray or implants paradoxically suppress gonadotrophin secretion and induce infertility (Fraser, 1982). GnRH agonists which are orally inactive except at excessively large doses would have significant advantages as a contraceptive for breast-feeding women. We have recently confirmed that the small amount of GnRH agonist which passes into the breast milk in breast-feeding women using the GnRH agonist nasal spray does not have any biological activity in the suckling infant (Dewart *et al.*, 1986).

Thus GnRH agonists, particularly as implants, offer a new, and potentially completely safe contraceptive for the breast-feeding mother and her baby.

## CONCLUSIONS

Breast feeding is associated with a variable period of amenorrhoea caused by a suckling-induced suppression of gonadotrophin (principally LH) secretion and consequent ovarian inactivity. The duration of this period of infertility is directly related to the strength of the suckling stimulus. Guidelines can be defined for the frequency and duration of breast feeds which will maintain infertility but these are not 100 per cent effective and they vary with the pattern of suckling

behaviour both within and between societies. Guidelines must, therefore, be established for each society and a global rule cannot probably be contemplated.

At the present time, the progestagen-only pill or implant appears to offer the most acceptable contraceptive for the breast-feeding mother. New developments of this and the use of GnRH agonists will hopefully provide more acceptable methods of contraception in the future.

Nevertheless, breast feeding continues to be a major importance in prolonging the interbirth interval on a global scale.

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# The 24 h pattern of pulsatile luteinizing hormone, follicle stimulating hormone and prolactin release during the first 8 weeks of lactational amenorrhoea in breastfeeding women

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**In women, breastfeeding results in a variable period of ovarian inactivity which is apparently related to suppression of the normal pulsatile release of luteinizing homone (LH). However, pulse profiles had only been studied during the daytime. Since resumption of pulsatile LH secretion during puberty is initiated at night, the present study determined the pattern of pulsatile LH secretion in relation to that of follicle stimulating hormone (FSH) and prolactin, and suckling and ovarian activity at 4 and 8 weeks postpartum in 20 fully breastfeeding women with lactational amenorrhoea. Blood samples were withdrawn at 10 min intervals for 24 h from 0900 h to 0900 h at either 4 weeks ($n$ = 9) or 8 weeks ($n$ = 11) postpartum, while the mothers and babies continued their normal pattern of suckling activity. At 4 weeks postpartum, no LH pulses occurred over 24 h in six of the nine women while one ($n$ = 1) or two ($n$ = 2) LH pulses occurred in three of the nine women. In contrast, LH pulses were present in nine of the 11 women at 8 weeks postpartum. The pulse frequency varied considerably from two to eight pulses over the 24 h and there was no influence of the time of day or sleep on the time of the pulse release. Lactational amenorrhoea was maintained for at least 10 weeks afterwards and there was no relationship between the time of resumption of ovarian activity and the presence or absence of pulsatile LH secretion at 4 or 8 weeks postpartum. Plasma concentrations of FSH increased from 4 to 8 weeks postpartum and were higher in women with than in women without LH pulses. In two women, clear pulses of FSH with a half-life of ~72 min were observed coincident with LH pulses. There was no difference in the suckling pattern or plasma concentrations of prolactin in women in whom pulsatile LH was or was not observed suggesting that prolactin *per se* was not involved in the suppression of pulsatile LH release. Assuming that each pulse of LH represented a pulse of gonadotrophin releasing hormone (GnRH) released from the hypothalamus, the present study suggests that during the period of total ovarian inactivity, suckling disrupts, but does not totally inhibit, the normal pattern of pulsatile GnRH release and hence release of LH and FSH from the pituitary. Thus, suckling maintains ovarian activity during lactational amenorrhoea by causing an abnormal pattern of gonadotrophin release that is insufficient to drive follicle development.**

*Key words:* pulsatile LH/lactational amenorrhoea/FSH/prolactin

## Introduction

Although breastfeeding plays an important role in the regulation of fertility, the mechanisms controlling the suppression of ovarian activity during lactation remain unclear (see McNeilly, 1988a, 1992). Previous studies (Glasier *et al.*, 1984a) have suggested that lactational infertility may be due to the inhibition of the pulsatile secretion of luteinizing hormone (LH). In those studies, the secretory pattern of LH was studied for only 7 h between 0900 h and 1700 h. However, the maintenance of night-time breastfeeding is associated with a prolonged duration of lactational infertility (Howie and McNeilly, 1982; McNeily *et al.*, 1985). In non-lactating women there is a significant diurnal variation in prolactin secretion with a nocturnal rise in prolactin concentrations which, if maintained during breastfeeding, may be of importance in suppressing ovarian activity. The prolactin response to suckling is greater during the evening and night than during the daytime (Glasier *et al.*, 1984b; Diaz *et al.*, 1989, 1991).

There may also be similarities between the resumption of ovarian activity during breastfeeding and those patterns observed at the onset of puberty where pulsatile LH secretion occurs initially only at night during sleep (Plant, 1988; Wu *et al.*, 1991). It is thus plausible that disturbances in the secretory pattern of gonadotrophins and prolactin may be responsible for the maintenance of infertility during lactation, but that these abnormalities are not apparent if the pattern of hormone release is studied only during daylight and waking hours.

The aim of the present study was to establish the 24 h secretory pattern of gonadotrophins and prolactin in relation to suckling pattern during the early part of the puerperium, at 4 and 8 weeks postpartum, when women were exclusively breastfeeding and amenorrhoeic.

## Materials and methods

### *Subjets and sampling methods*

The study was approved by the Lothian Health Board Ethics Committee. Full details of the longitudinal study were explained to all the potential recruits while they were still in the postnatal ward of the Simpson Memorial Maternity Pavilion (SMMP),

Royal Infirmary, Edinburgh, and they were given a detailed information sheet about the study. The women were then contacted by telephone after discharge from hospital to allow them time to discuss participation in the study with husbands and friends. If they decided to volunteer for the study, they were visited in their own homes when a written informed consent was obtained with the understanding that they could withdraw from the study at any time.

The mothers chose their intended feeding practices following the advice of their midwives and health visitors. Health care for the mothers and infants was provided by their own general practitioners and apart from the interest obtained from taking part in the study no benefits would accrue to the women taking part. There were no financial reimbursements for taking part in the study.

Twenty-four hour secretory patterns of gonadotrophin were investigated in 20 breastfeeding women at either 4 ($n = 9$; Group 1) or 8 ($n = 11$; Group 2) weeks postpartum. All the women were amenorrhoeic at the time of investigation. The infant feeding pattern was recorded daily in a diary, the total number of suckling episodes over 24 h was recorded daily. Night-time suckling episodes were defined as those which occurred between 2200 h and 0600 h and were recorded separately from daytime feeding episodes. The average duration of the suckling episodes was recorded in minutes. Any supplementary food other than breast milk given to the baby was recorded. Supplementary feeds were defined as formula or cow's milk feed from a bottle or cup, or any feed of solid food. Forty-eight hours prior to admission to the Research Unit for serial blood sampling, a more detailed infant feeding chart was completed. In addition to the suckling frequency and duration, the exact timing of each suckling episode throughout the 48 h prior to admission was recorded.

The women were admitted with their infants to the Research Unit of the SMMP. While in the Unit, no restrictions were made on physical activity or food intake beyond that placed by a hospital environment, and women slept at night according to their usual pattern. Breastfeeding took place on demand. The activity of the mothers was recorded by observation, including meal times, times and duration of breastfeeding and sleep pattern. Lights were switched off between 2300 h and 0700 h. On admission to the unit, a 20 G Venflon intravenous cannula was inserted into a forearm vein at ~0900 h and a 2.5 ml sample of venous blood was collected every 10 min throughout 24 h; the plasma was separated and stored at −20°C and later assayed for LH, follicle stimulating hormone (FSH) and prolactin. At night during sleep, the blood samples were collected through a long intravenous catheter which passed through a hole in the wall to the adjoining laboratory, allowing blood samples to be collected without disturbing the women's sleep.

Ovarian activity was monitored by the measurement of urinary oestrone glucuronide and pregnanediol glucuronide in weekly urine samples from 2 weeks postpartum for the duration of the sampling period until the first ovulatory cycle.

### *Hormone assays*

Plasma concentrations of LH and FSH were measured by radioimmunoassay as described previously (Djahanbakhch *et al.*, 1981; Hunter and Bennie, 1979) while plasma prolactin was measured in a two-site immunoradiometric assay (NETRIA, St. Bartholomew's Hospital, London; Wu *et al.*, 1990). The intra- and inter-assay coefficients of variation were <8% and <11% respectively for LH, FSH and prolactin. Concentrations of oestrone glucuronide and pregnanediol glucuronide in urine were measured as described previously and corrected for the amount of creatinine in each sample (Fraser *et al.*, 1989). All urine samples were assayed in one group with an intra-assay variation of <10%.

### *Statistical analysis*

The data are presented as the mean ± SEM except where otherwise stated. Comparisons between mean hormonal concentrations and the various parameters of pulsatile LH secretion were performed using Student's unpaired *t*-test on log-transformed data. Significant hormone pulses were identified using the 'MUNRO' pulse analysis program (Zaristow Software, Haddington, Scotland EH14 4PD) which is based on the Pulsar algorithm (Merriam and Wachter, 1982). To identify an LH peak, the algorithm was adjusted to require a threshold of two standard deviations (SD) above the baseline with a minimum pulse interval of 30 min. A 30 min smoothing window was used to generate the moving average in the baseline calculation. The nadir window was 30 min and the rise threshold (in SD units) to which the peak must rise above the nadir was 0.5. The mean pulse frequency, pulse amplitude, pulse area and nadir levels of LH release were compared between the different groups of women.

## Results

### *Comparison of suckling pattern and ovarian activity at 4 and 8 weeks postpartum*

The mean number of suckling episodes and suckling duration during the week prior to the day when the pulse bleed was undertaken are shown for both groups of women in Table I. All the women were fully breastfeeding at the time of the investigation. There was no statistically significant difference in the timing of the eventual introduction of supplementary food nor in the total duration of lactational amenorrhoea between the two groups of women.

While there was no difference in the total amount of time that the baby spent at the breast during 24 h (suckling duration), the women who were studied at 8 weeks postpartum were giving significantly ($P < 0.05$) fewer breastfeeds (suckling frequency) than those studied at 4 weeks postpartum (6.47 ± 0.40 versus 8.30 ± 0.66 episodes/24 h). This reduction in suckling episodes was accounted for by a decline in night-time feeds which occurred significantly ($P < 0.01$) less often by the eighth postpartum week (1.42 ± 0.20 episodes/24 h compared with 2.49 ± 0.32 episodes/24 h at 4 weeks). The mean urinary oestrone-3-glucuronide excretion at 4 weeks postpartum (24.45 ± 5.33 μg/g creatinine) was not significantly different from that at 8 weeks postpartum (20.01 ± 2.57 μg/g creatinine; Table I).

### *Comparison of mean LH, FSH and prolactin concentrations at 4 and 8 weeks*

The mean ± SEM plasma concentrations of LH, FSH and prolactin for the 20 individual women were calculated from the

Table I. Comparison of suckling pattern and ovarian activity (mean ± SE) at 4 and 8 weeks postpartum in fully breastfeeding women and the subsequent time of introduction of supplements and duration of amenorrhoea

| | Time postpartum | |
|---|---|---|
| | 4 weeks ($n$ = 9) | 8 weeks ($n$ = 11) |
| Urinary oestrone glucuronide (μg/g creatinine) | 24.45 ± 5.33 | 20.01 ± 2.57 |
| Urinary pregnanediol glucuronide (μg/g creatinine) | 0.53 ± 0.08 | 0.51 ± 0.07 |
| No. of suckling episodes (24 h) | 8.30 ± 0.66 | 6.47 ± 0.40* |
| Suckling duration in min (24 h) | 137.46 ± 12.89 | 143.70 ± 15.81 |
| No. of suckling episodes (day) | 5.92 ± 0.39 | 5.05 ± 0.29 |
| Suckling duration in min (day) | 97.84 ± 10.31 | 112.14 ± 12.54 |
| No. of suckling episodes (night) | 2.49 ± 0.32 | 1.42 ± 0.20** |
| Suckling duration in min (night) | 39.62 ± 4.09 | 31.57 ± 5.40 |
| Time of introduction of supplements (weeks postpartum) | 16.29 ± 1.70 | 15.18 ± 1.03 |
| Duration of amenorrhoea (weeks postpartum) | 33.71 ± 5.44 | 33.36 ± 4.48 |

*$P < 0.05$, **$P < 0.01$.

Table II. Mean (±SE) plasma concentrations of prolactin, follicle stimulating hormone (FSH) and luteinizing hormone (LH) and the characteristics of pulsatile LH secretion over a 24 h period at 4 weeks postpartum in fully breastfeeding women. The urinary concentration of oestrone glucuronide in an early morning urine specimen on the day of sampling is also given

| Subjects | Prolactin (U/l) | FSH (U/l) | Urinary oestrone glucuronide (μg/g creatinine) | LH (U/l) | LH pulse parameters | | | |
|---|---|---|---|---|---|---|---|---|
| | | | | | No. of pulses (per 24 h) | Inter-pulse interval (min) | Pulse amplitude (U/l) | Pulse area (U/l) |
| 1 | 1905 ± 156 | 2.30 ± 0.30 | 14.67 | 1.16 ± 0.02 | None | – | – | – |
| 2 | 1237 ± 109 | 0.93 ± 0.02 | 20.62 | 2.71 ± 0.02 | None | – | – | – |
| 3 | 1214 ± 84 | 1.12 ± 0.03 | 18.86 | 2.11 ± 0.02 | None | – | – | – |
| 4 | 2631 ± 254 | 2.23 ± 0.05 | 13.58 | 3.98 ± 0.05 | None | – | – | – |
| 5 | 1454 ± 67 | 2.01 ± 0.04 | 21.52 | 3.28 ± 0.03 | None | – | – | – |
| 6 | 2259 ± 39 | 2.16 ± 0.04 | 24.45 | 1.82 ± 0.03 | None | – | – | – |
| 7 | 3686 ± 38 | 2.10 ± 0.05 | 19.74 | 2.55 ± 0.07 | 2 | 440 | 2.48 ± 0.44 | 184 ± 32 |
| 8 | 2584 ± 156 | 2.63 ± 0.09 | 60.44 | 2.54 ± 0.08 | 2 | 210 | 1.84 ± 0.45 | 162 ± 59 |
| 9 | 4927 ± 68 | 4.34 ± 0.11 | 26.14 | 2.84 ± 0.05 | 1 | – | 1.63 | 409 |

Table III. Mean (±SE) plasma concentrations of prolactin, follicle stimulating hormone (FSH) and luteinizing hormone (LH) and the characteristics of pulsatile LH secretion over a 24 h period at 8 weeks postpartum in fully breastfeeding women. The urinary concentration of oestrone glucuronide in an early morning urine specimen on the day of sampling is also given

| Subjects | Prolactin (U/l) | FSH (U/l) | Urinary oestrone glucuronide (μg/g creatinine) | LH (U/l) | LH pulse parameters | | | |
|---|---|---|---|---|---|---|---|---|
| | | | | | No. of pulses (per 24 h) | Inter-pulse interval (min) | Pulse amplitude (U/l) | Pulse area (U/l) |
| 10 | 1268 ± 35 | 2.75 ± 0.09 | 20.00 | 1.66 ± 0.03 | None | – | – | – |
| 11 | 3515 ± 165 | 0.93 ± 0.04 | 13.97 | 1.48 ± 0.03 | None | – | – | – |
| 12 | 2019 ± 133 | 4.32 ± 0.11 | 10.86 | 3.49 ± 0.20 | 2 | 340 ± 94 | 10.87 ± 1.38 | 673 ± 222 |
| 13 | 1514 ± 103 | 6.64 ± 0.11 | 15.56 | 2.61 ± 0.06 | 5 | 257 ± 26 | 1.25 ± 0.16 | 88 ± 9 |
| 14 | 3380 ± 165 | 4.39 ± 0.07 | 9.91 | 2.94 ± 0.07 | 2 | 160 | 1.17 ± 0.19 | 173 ± 109 |
| 15 | 5416 ± 224 | 3.38 ± 0.06 | 19.90 | 4.81 ± 0.25 | 4 | 270 ± 5 | 7.22 ± 3.94 | 477 ± 296 |
| 16 | 1307 ± 59 | 4.96 ± 0.11 | 22.01 | 6.12 ± 0.21 | 2 | 550 | 4.38 ± 1.58 | 324 ± 198 |
| 17 | 938 ± 49 | 2.69 ± 0.06 | 30.26 | 3.77 ± 0.15 | 7 | 147 ± 36 | 3.38 ± 0.71 | 204 ± 44 |
| 18 | 1213 ± 106 | 5.12 ± 0.06 | 18.46 | 6.05 ± 0.14 | 8 | 186 ± 41 | 3.74 ± 0.35 | 223 ± 24 |
| 19 | 3389 ± 113 | 4.04 ± 0.12 | 35.17 | 4.22 ± 0.17 | 4 | 180 ± 48 | 5.36 ± 1.48 | 339 ± 134 |
| 20 | 812 ± 68 | 5.04 ± 0.16 | 23.61 | 1.63 ± 0.04 | 3 | 470 ± 147 | 1.26 ± 0.09 | 128 ± 55 |

144 samples obtained during the 24 h of serial blood sampling. Results for Group 1 studied at 4 weeks postpartum are shown in Table II and for Group 2 studied at 8 weeks postpartum in Table III.

The mean concentrations of LH, FSH and prolactin for both groups of women are shown in Table IV. The overall mean concentration of LH at 4 weeks postpartum was not statistically significantly different from the mean LH concentration at 8 weeks postpartum. Similarly the mean prolactin concentrations were not significantly different when the two time periods were compared. In contrast, the overall mean FSH concentration at 8 weeks postpartum (4.02 ± 0.46 U/l) was significantly ($P < 0.05$)

higher than the mean FSH concentration at 4 weeks postpartum (2.20 ± 0.32 U/l).

### *Individual 24 h secretory patterns of LH*

The various parameters of the individual pulsatile LH secretion in the two groups of women are shown in Tables II and III. At 4 weeks postpartum, the 24 h LH secretory pattern showed a complete absence of statistically identifiable pulses of secretion in six of the nine women studied (Table II). In the other three women, there was a return of pulsatile LH secretion although there were no more than two statistically significant LH pulses over the 24 h as detected by the 'Munro' computerized algorithms (Table II).

Figure 1 shows the 24 h secretory pattern in two women at 4 weeks postpartum. In Subject 1, the LH secretory pattern was fully suppressed and non-pulsatile. In contrast, the LH secretory pattern of Subject 7 showed a return of LH pulsatility which was characterized by a slow frequency (2 pulses/24 h) and small amplitude (2.48 ± 1.00 U/l). In contrast, at 8 weeks postpartum, nine of the eleven women studied showed a return of pulsatile LH secretion (Table III). Only two women had a fully suppressed LH secretory pattern. All the women were amenorrhoeic and the ovarian activity was completely suppressed as shown by the low level of urinary excretion of both oestrone (Table III) and pregnanediol. Figure 2 shows the LH secretory profiles in two women at 8 weeks postpartum. Subject 10 had a fully suppressed LH secretory pattern. In Subject 17, seven statistically significant LH pulses were detected over 24 h with a mean LH pulse amplitude of 3.38 ± 1.00 U/l.

### *Comparison of the pulsatile secretion of LH at 4 and 8 weeks postpartum*

The mean concentration of LH and the various parameters of pulsatile LH secretion in the two groups of women are shown in Table IV. Although there was no statistically significant difference in mean LH concentration at 4 and 8 weeks postpartum, the 24 h secretory patterns were significantly different as characterized by the gradual return of pulsatile LH secretion. The LH pulse frequency was significantly ($P < 0.05$) increased at 8 weeks postpartum (3.36 ± 0.78/24 h) compared with the frequency at 4 weeks postpartum (0.56 ± 0.29/24 h). However, the LH pulse amplitude, pulse area or nadir between pulses was not significantly different at 4 and 8 weeks postpartum (Table IV).

### *Comparison of women with pulsatile and non-pulsatile LH secretory patterns and pulsatile secretion of FSH*

Ignoring the time postpartum, the 20 women were divided into two groups according to the presence or absence of pulsatile LH secretion, to determine whether there was any difference in the

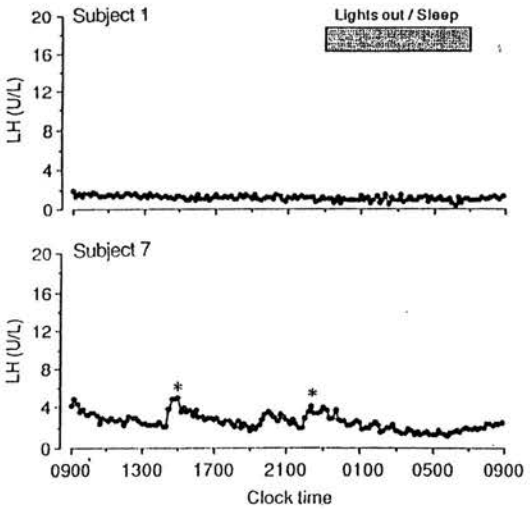


**Fig. 1.** Changes in the plasma concentrations of luteinizing hormone (LH) over a 24 h period at 4 weeks postpartum in two fully breastfeeding women. The asterisks indicate a significant pulse of LH.

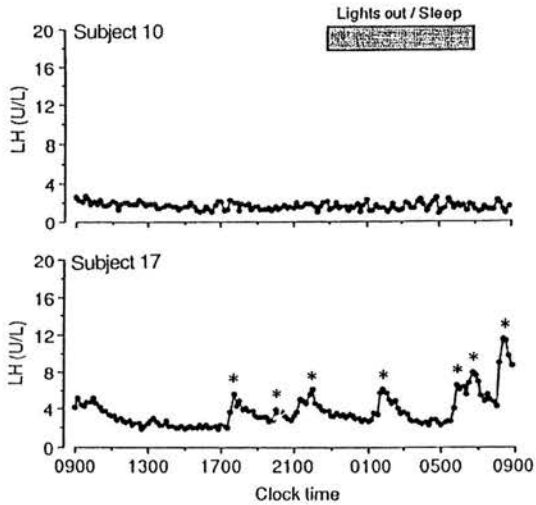


**Fig. 2.** Changes in the plasma concentrations of luteinizing hormone (LH) over a 24 h period at 8 weeks postpartum in two fully breastfeeding women. The asterisks indicate a significant pulse of LH.

**Table IV.** Comparison of mean concentrations (mean ± SE) of follicle stimulating hormone (FSH), prolactin and luteinizing hormone (LH) and the characteristics of the pulsatile secretion of LH at 4 and 8 weeks postpartum in fully breastfeeding women

| | Time postpartum | |
|---|---|---|
| | 4 weeks ($n$ = 9) | 8 weeks ($n$ = 11) |
| Mean FSH (U/l) | 2.20 ± 0.32 | 4.02 ± 0.46* |
| Mean prolactin (mU/l) | 2433 ± 409 | 2252 ± 442 |
| Mean LH (U/l) | 2.55 ± 0.27 | 3.53 ± 0.50 |
| LH pulses absent | 6 | 2 |
| LH pulses present | 3 | 9 |
| LH pulse frequency (per 24 h) | 0.56 ± 0.29 | 3.36 ± 0.78* |
| LH pulse amplitude (U/l) | 1.98 ± 1.26 | 3.93 ± 0.82 |
| LH pulse area (U/l) | 252 ± 79 | 292 ± 62 |
| LH pulse nadir (U/l) | 2.01 ± 0.49 | 2.78 ± 0.52 |

*$P < 0.05$ compared to 4 weeks postpartum.

plasma concentrations of FSH or prolactin, the suckling and ovarian activity and the subsequent duration of amenorrhoea in women who resumed compared to women who had not resumed pulsatile LH secretion. Eight women had a non-pulsatile LH secretory pattern while 12 women had a pulsatile profile. Table V shows the mean suckling frequency and duration in the two groups of women. There was no statistically significant difference in the suckling pattern in the two groups or in the time of introduction of supplementary food or in the total duration of postpartum amenorrhoea. In spite of the return of pulsatile LH secretion, there was no statistically significant difference in the mean urinary oestrone and pregnanediol excretions in the two groups of women, indicating no return of ovarian activity.

Table V. Comparison of the pattern of suckling and ovarian status (mean ± SE) assessed by the urinary concentrations of oestrone glucuronide and pregnanediol glucuronide in fully breastfeeding women at 4 and 8 weeks in whom pulsatile secretion of luteinizing hormone (LH) either had not ($n$ = 8) or had returned ($n$ = 12). The subsequent time of introduction of supplements and duration of amenorrhoea for these women is also shown

| | No LH pulses ($n$ = 8) | LH pulses ($n$ = 12) |
|---|---|---|
| No. of suckling episodes (per 24 h) | 7.4 ± 0.6 | 7.2 ± 0.6 |
| Suckling duration in min (per 24 h) | 139 ± 15 | 142 ± 14 |
| No. of suckling episodes (day) | 5.4 ± 0.4 | 5.5 ± 0.3 |
| Suckling duration in min (day) | 99 ± 12 | 110 ± 12 |
| No. of suckling episodes (night) | 2.2 ± 0.2 | 1.7 ± 0.03 |
| Suckling duration in min (night) | 40 ± 4 | 32 ± 5 |
| Oestrone glucuronide (μg/g creatinine) | 18.7 ± 1.4 | 24.4 ± 3.9 |
| Pregnanediol glucuronide (mg/g creatinine) | 0.49 ± 0.07 | 0.53 ± 0.07 |
| Introduction of supplement (weeks) | 15.4 ± 1.2 | 15.7 ± 1.13 |
| Duration of amenorrhoea (weeks) | 38.2 ± 5.3 | 30.5 ± 4.7 |

The mean LH concentration was significantly ($P < 0.01$) higher in the women with than in those without a pulsatile pattern of secretion (3.63 ± 0.41 U/l versus 2.27 ± 0.34 U/l). Although the mean prolactin concentration was higher in the pulsing group when compared with the non-pulsing group (2599 ± 451 U/l versus 1936 ± 292 U/l), the difference did not reach statistical significance.

The mean FSH concentration was significantly higher ($P < 0.001$) in the pulsatile group (4.14 ± 0.37 U/l) compared with the non-pulsatile group (1.81 ± 0.25 U/l). In addition, pulses of FSH were identified during two periods of sampling, one at 4 weeks and one at 8 weeks postpartum in women in whom pulsatile LH secretion had returned (Figure 3). No pulses of FSH could be identified in the other 10 women in whom pulsatile LH secretion had resumed (e.g. Figure 3d). The start of each pulse of FSH coincided exactly with the start of an LH pulse (Figure 3). The limited numbers of pulses in two women did not allow a proper statistical evaluation of pulse parameters, but overall the first decay component of each pulse suggested a mean half-life of ~72 ± 5.8 min ($n$ = 5 pulses) with a second component of 160 min (2 pulses).

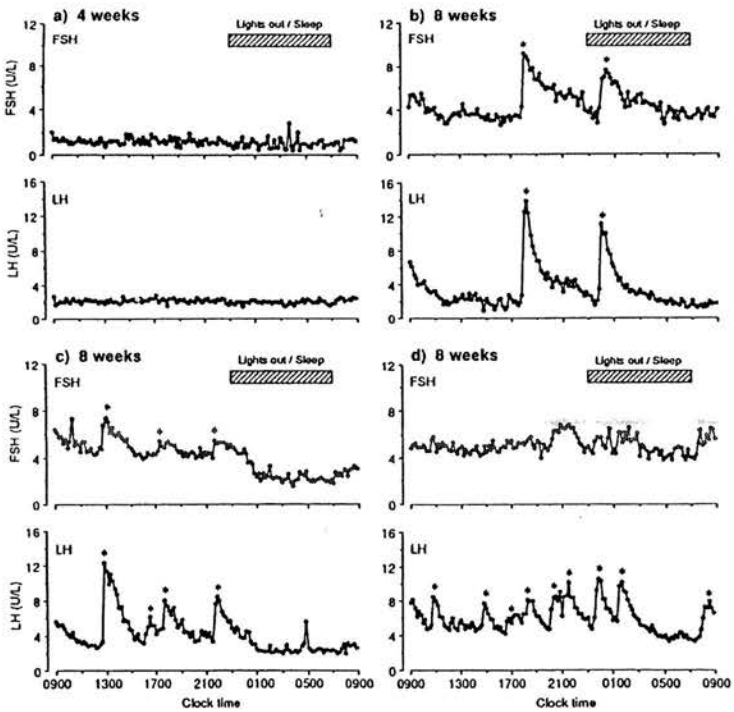


Fig. 3. Changes in the plasma concentrations of follicle stimulating hormone (FSH) and luteinizing hormone (LH) in fully breastfeeding women at 4 weeks (a) and 8 weeks (b–d) postpartum. The asterisks indicate significant pulses of FSH or LH.

## Discussion

In women who are breastfeeding and not using contraception, lactational infertility can be divided into three main phases before the onset of the next pregnancy: (i) the initial recovery from pregnancy, (ii) the period of lactational amenorrhoea and (iii) a period when menstruation returns associated with inadequate or adequate corpus luteum function (McNeilly, 1988a, 1992). In bottle-feeding women, the resumption of menstruation occurs at around 8 weeks postpartum (Gray *et al.*, 1987; Howie and McNeilly, 1982; Howie *et al.*, 1982b). Therefore there appears to be a finite period after pregnancy during which the hypothalamo–pituitary–ovarian axis takes time to recover from the effects of pregnancy, even in the absence of breastfeeding. Thereafter, the suppression of ovarian activity during lactational amenorrhoea is maintained only if the infant is being breastfed. The aim of our study was to establish the 24 h secretory pattern of gonadotrophins and prolactin in relation to suckling activity and time postpartum during lactational amenorrhoea. At 4 weeks postpartum, we would expect ovarian activity to be suppressed due to time for recovery from the effects of pregnancy, regardless of the infant feeding method; at 8 weeks an increase in gonadotrophin secretion, particularly pulsatile LH secretion, may occur since suckling activity may decline even though amenorrhoea is maintained (Howie and McNeilly, 1982; McNeilly *et al.*, 1985).

Although all the twenty women taking part in the study were fully breastfeeding at the time of the pulse study, there was, nevertheless, a significant difference in infant feeding patterns over the 4 week interval. By the eighth postpartum week there had been a decline in the average number of suckling episodes over 24 h as a result of a reduction in the number of night feeds, the frequency of feeding episodes during the day remaining unchanged. Moreover, despite a fall in suckling frequency, the total duration of breastfeeding over 24 h, i.e. the total duration of the suckling stimulus, was maintained. These findings support those of Howie *et al.* (1981, 1982a) who described an early reduction in night-time feeds and observed that when the number of suckling episodes was reduced (in this case with the introduction of supplementary feeds) the suckling duration tended to be maintained for at least some weeks. It would seem that while the mothers are quick to impose a more sociable and convenient pattern of feeding on the baby, the child itself manages to take in the desired amount of milk by spending longer over each feed, confirming our previous reports in women in Edinburgh (Howie *et al.*, 1982a,b; Glasier *et al.*, 1983; McNeilly *et al.*, 1985).

Despite a change in the character of the suckling stimulus between 4 and 8 weeks postpartum, there was no significant change in overall plasma concentrations of prolactin, confirming our previous observations (Howie *et al.*, 1982a; Glasier *et al.*, 1984b). Moreover, the alteration in suckling patterns appeared to have no effect on ovarian activity, as reflected both by continuing amenorrhoea and by the lack of ovarian activity indicated by the extremely low concentrations of urinary oestrone and pregnanediol glucuronide.

Although we were unable to demonstrate any differences in mean basal concentrations of LH between the women bled at 4 and 8 weeks postpartum, there were clear differences in the pulsatile pattern of secretion of LH. Pulses of LH only occurred in three of the nine women at 4 weeks postpartum and only one or two pulses occurred in the 24 h, although the amount of LH released in each pulse appeared to be similar to that at 8 weeks. However, by 8 weeks after delivery, nine of the 11 women showed the occasional statistically significant pulse of LH secretion during the 24 h period although the frequency varied considerably between two and eight pulses in the 24 h. These results are at variance with a recent report in which low-amplitude pulses of LH at a normal follicular phase frequency of around one pulse per hour appeared to occur in all fully breastfeeding women at 3 weeks and 3 months postpartum (Nunley *et al.*, 1991). The reason for this discrepancy is not known since in both studies ovarian activity was fully suppressed. It may be that the difference is due to the different assay methods employed in the two studies. In previous studies using the same radioimmunoassay as in the present study, an absent or reduced LH pulse frequency was also observed in women in the early postpartum period (Glasier *et al.*, 1984a). It is of interest that LH pulses were released at apparently random intervals throughout the 24 h. There was no enhanced release of LH as seen during puberty (Plant, 1988; Wu *et al.*, 1991) suggesting that the inhibition of GnRH output by suckling and the subsequent gradual release from this inhibition may not be equivalent in mechanism to that occurring during puberty.

It is clear from our results in the present study that, even though pulsatile secretion of LH may resume, the frequency of LH pulses would not be expected to represent an adequate signal to cause resumption of ovarian activity (Crowley *et al.*, 1985; Lincoln *et al.*, 1985). We have been able to induce follicle growth and ovulation during lactational amenorrhoea by treatment of breastfeeding women at 6 weeks postpartum with a constant 90 min frequency of pulsatile GnRH (Glasier *et al.*, 1986). Thus, it appears that the ovarian inactivity which causes lactational amenorrhoea is due to a suckling-induced disruption of the release of GnRH from the hypothalamus at the normal frequency occurring during the follicular phase of the menstrual cycle (Backstrom *et al.*, 1982; Crowley *et al.*, 1985). In the present study, the presence or absence of LH/GnRH pulses at 8 weeks did not predict the time of resumption of ovarian activity.

The mechanism by which the suckling stimulus disrupts the pattern of GnRH output from the hypothalamus remains unknown (McNeilly, 1988a, 1992). While the high plasma concentrations of prolactin associated with lactation have been correlated with the duration of lactational amenorrhoea (Duchen and McNeilly, 1980; Robyn and Meuris, 1982; Gross and Eastman, 1985; McNeilly *et al.*, 1985; Diaz *et al.*, 1989, 1991; Fink *et al.*, 1992), there is no clear evidence that prolactin is the causal agent in suppression of GnRH (McNeilly, 1987). Indeed, in the present study, plasma concentrations of prolactin were the same or even higher in women in whom LH pulses had resumed than in those in whom no pulses were occurring. This, together with the observation that pulses of LH occurred at random throughout the day, including during sleep when prolactin concentrations are at their highest, suggests that prolactin *per se* is not implicated in the suckling-induced suppression of hypothalamic GnRH output

at least in the early postpartum period in fully breastfeeding women.

In addition to the difference in LH pulsatility, we were able to demonstrate a significant increase in basal FSH concentration by 8 weeks postpartum. This supports previous studies (Rolland *et al.*, 1975; Delvoye *et al.*, 1980; Glasier *et al.*, 1983; Kremer *et al.*, 1991; Nunley *et al.*, 1991) which were unable to define a role for disturbances of FSH secretion in the maintenance of lactational amenorrhoea. It was also clear that plasma concentrations of FSH were significantly higher in women in whom pulsatile secretion of LH had resumed, confirming many previous observations that GnRH is important in the maintenance of FSH secretion (see McNeilly, 1988b). Of considerable interest was the observation in two women of clear pulses of FSH apparently released in response to GnRH since LH was released coincidently with each pulse of FSH. The first phase half-life of 60 to 90 min calculated from the pulses of FSH was within the range previously reported for the clearance of endogenous FSH after hypophysectomy (Yen *et al.*, 1970) but somewhat shorter than for exogenous FSH prepared from urine (Diczfalusy and Harlin, 1988). It has been suggested that the absence of ovarian steroids in juveniles, men and postmenopausal women results in the release from the pituitary of acidic forms of FSH with a long half-life (Wide and Wide, 1984). It is interesting in the present study that the FSH released had a relatively short half-life since these women had low levels of ovarian steroids at a concentration which was equivalent to that in postmenopausal women (Fraser *et al.*, 1989). Low-amplitude pulses of FSH have only been observed infrequently during the menstrual cycle (Backstrom *et al.*, 1982), the long half-life and slow clearance making it difficult to observe pulses. It is interesting that we observed FSH pulses in the present study when there was little negative feedback on the pituitary due to the low concentrations of ovarian steroids and that, as the frequency of LH/GnRH pulses increased, so the amplitude of the FSH pulses was decreased while the mean plasma concentrations of FSH increased. These results suggest that the pattern of GnRH input may alter the release of FSH independently of the normal negative feedback control of FSH secretion (see McNeilly, 1988b).

In conclusion, it would appear that by 2 months after delivery, while ovarian activity remains suppressed in fully breastfeeding women, pulsatile secretion of LH has resumed at a low and varying frequency in the majority of women. Assuming that each pulse of LH represents a pulse release of GnRH from the hypothalamus, our results suggest that the suckling stimulus does not totally inhibit GnRH output, but disrupts the normal pattern of release. While the resumption of GnRH is also associated with an increase in FSH concentrations to within the range normally occurring in the follicular phase, the presence of a grossly disturbed pattern of LH secretion results in ovarian activity remaining suppressed. Whether the resumption of even this small amount of pulsatility is a result of the passage of time or of a change in the suckling stimulus remains to be determined. There may be some aspect of the suckling stimulus, such as suckling intensity, which also changes with time and which we were unable to measure. However, the observation that prolactin concentrations, reflecting the suckling stimulus, remained unchanged suggests that time postpartum may be associated with the return of pulsatile secretion of GnRH.

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# Physiological Mechanisms Underlying Lactational Amenorrhea

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## INTRODUCTION

Although there may be dispute over the best way of implementing the contraceptive effects of breastfeeding into family planning strategies it is an irrefutable fact that breast feeding profoundly inhibits reproductive function.[1,2] The problem with providing exact guidelines for the use of breastfeeding as an absolutely reliable contraceptive on an subject to subject basis is due to the very nature of the driving force of the suppression of fertility, the baby itself. The degree of suppression of ovarian activity is related to the strength of the suckling stimulus, which is an uncontrollable variable related to the nature of the sucking activity of the baby and the sensitivity of the mother to this sucking activity. If the baby sucks well and the mother activates the milk ejection reflex quickly then the baby receives the required amount of milk quickly. However, this quick suckling activity which provides the required nutrition for the infant may not be sufficient to maintain complete suppression of the pituitary-gonadal axis with a consequent early return of fertility. Attempts to overcome these problems of variation in suckling activity by maintaining or increasing suckling activity are unlikely to succeed since the baby appears to adjust the suckling activity to maintain a reasonably constant nutrient intake. Thus, increasing suckling frequency in an attempt to prolong the period of infertility in breastfeeding women in Santiago, Chile failed because the infants suckled for a shorter time at each feed maintaining a similar overall suckling stimulus throughout the 24h period.[3]

A further confounding issue is the impact of giving supplementary nutrition to the infant. In some societies the nutrient value of this supplement is low, it is introduced gradually and, where suckling frequencies are normally high the impact on overall suckling patterns may not have a major effect on the suppression of fertility.[4,5] In other societies where high calorie supplements are introduced this may have a dramatic effect on suckling patterns as we found in Edinburgh where babies reduced the duration of each breastfeed without reducing the number of feeds per day.[4] The consequence of this decline in overall suckling activity was an earlier return of fertility. This enormous variation in the patterns of suckling and effects of introduction of supplements has deflected attention from the fact that suckling has a powerful inhibitory effect on



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ovarian activity which occurs in all women. The major purpose of this short review is to summarize our knowledge on the mechanisms by which the suckling stimulus inhibits ovarian activity. As a preliminary it is important to review recent studies on the other two major components of suckling, the release of prolactin, which is essential for maintaining milk production, and the release of oxytocin, which ejects the milk from the breast.

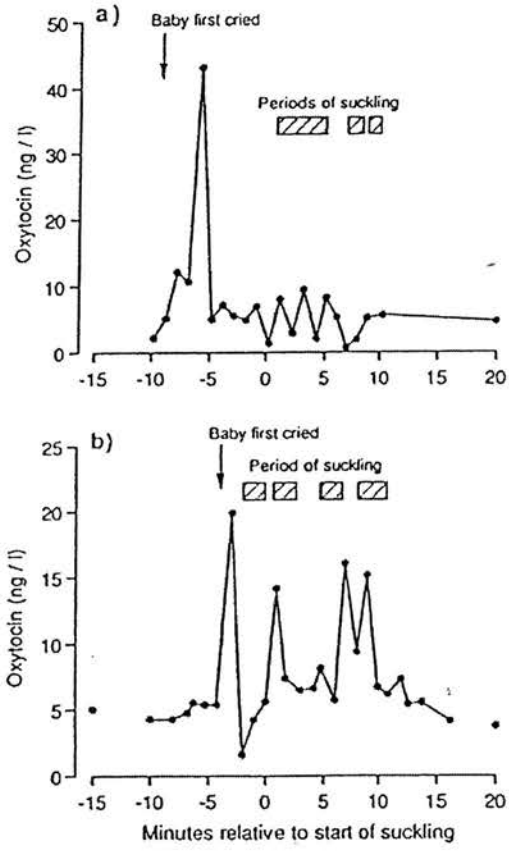


FIGURE 1. Changes in the plasma concentrations of oxytocin before and during suckling (▨) in two women at a) 4 days and b) 28 days postpartum. Note the increase in oxytocin before the onset of suckling (from ref. 6).

## SUCKLING AND OXYTOCIN RELEASE

Remarkably little attention has been paid to the importance of oxytocin in lactation. In women only 20–30% of the normal volume of milk at any feed is released in the absence of oxytocin release.

While oxytocin is released in response to nipple stimulation[6–8] a major release of oxytocin occurs before the onset of suckling (FIG. 1).[6] Spontaneous, regular release of oxytocin may also occur throughout lactation in the absence of suckling.[9] Oxytocin release is very sensitive to inhibition particularly by stress,[10] and any inhibition of oxytocin release would lead to major problems in either initiating or maintaining lactation and may be a cause of lactation failure in women. Treatment with nasal oxytocin has resulted in a dramatic improvement in milk production, indirectly, by

allowing release of stored milk and continuation of normal prolactin-induced milk production.[11] The failure to empty the breast adequately may lead to reduction in the capacity of the breast to produce milk due to the presence of local paracrine factors within the breast which modulate milk production.[12]

In the vast majority of cases, particularly where breastfeeding is the accepted norm, a lack of oxytocin release is not likely to be a major problem. However, it may be that in tentative mothers trying to establish breastfeeding with little support, the potential stress involved may prevent adequate oxytocin release, reduce milk production, amplify the stress level with further inhibition of oxytocin release and so the downward spiral of failure of lactation proceeds. Intervention with oxytocin, or correct counselling and support while establishing breastfeeding should overcome these problems.

## PROLACTIN RELEASE

The plasma concentration of prolactin increases progressively throughout pregnancy associated with an increase in pituitary size.[13,14] At term, concentrations of prolactin are between 10 and 100 times higher than during the normal menstrual cycle and remain elevated for up to 3 weeks postpartum even in the absence of suckling.[14] Prolactin is the essential hormone for milk production in women; absence of prolactin, either due to treatment with bromocriptine[15] or in hypopituitary patients[16] leads to failure of milk production. Thus, at term prolactin concentrations are sufficiently high in almost all women to initiate lactation although there is no correlation between the prolactin response to suckling or basal plasma concentrations of prolactin and the time to onset of milk production or the amount of milk produced.[17] Prolactin is released in response to the suckling stimulus of the baby and there is no evidence of release before the onset of nipple stimulation.[6] While prolactin may be released during removal of milk by breast pumps, the amount released is very variable and may be the cause of the variable success of maintaining lactation with these pumps. A prolactin response equivalent to that induced by a suckling baby was only induced with an electrical pulsatile pump.[8] There is no close correlation between plasma concentrations of prolactin, either basal or amounts released during a suckling episode, and the amount of milk produced throughout lactation.[7,14] This suggests that adequate amounts of prolactin are available at all times throughout lactation. Nevertheless treatment of women with dopaminergic antagonists which increase plasma concentrations of prolactin do lead to an increase in milk production.[18,19] However, since these drugs have been used in women in whom milk yields were low, and since these drugs potentially can act as tranquillizers it may be pertinent to question whether they may act by reducing stress and increasing oxytocin release in these women, thus working indirectly to increase milk production. It does appear that in most lactations the suckling infant induces sufficient prolactin release to maintain lactation.

An increase in prolactin occurs within minutes of the onset of suckling and release may continue for 20 to 40 minutes, apparently regardless of the duration of the suckling stimulus.[20] There is no change in the half-life or form of the prolactin released during lactation.[21] From at least 4 weeks postpartum the sleep-associated increase in prolactin which occurs in non-lactating women resumes[21,22] and the prolactin response to the suckling is greater at night than during the day.[20,22,23] This increase in prolactin release is apparently not due to any change in the suckling activity of the baby,[20] suggesting that this may relate to a decrease in hypothalamic dopaminergic tone during sleep which causes the sleep-induced increase in prolactin. Prolactin

release during lactation remains under dopaminergic but not opioid inhibition. Treatment of breastfeeding women with the dopaminergic antagonist metoclopramide caused a 20- to 30-fold increase in prolactin release, some 8 times the maximum elicited by suckling indicating a profound dopaminergic inhibition of release.[24] In contrast, treatment with the opiate antagonist naloxone was without effect[24] confirming previous studies in women,[25-27] although in monkeys prolactin release is dependent on opioids.[28] Progesterone[29] but not the synthetic progestagen norethisterone[24] enhanced the prolactin response to suckling.

Although there is no doubt that prolactin is required for milk production, the potential role for prolactin in causing the infertility associated with suckling remains very unclear. Studies in animals do not support any major direct role for prolactin in lactational infertility. An increased release of prolactin in response to suckling over a 24h period was observed in women with prolonged lactational amenorrhea,[23,30] although we could not confirm this observation.[22] The apparently close correlation between the duration of hyperprolactinemia and duration of lactational amenorrhea[31,32] suggested a role for prolactin. However, it is more likely that since the plasma concentration of prolactin depends on the frequency and duration of suckling, the hyperprolactinaemia reflects suckling activity and that the true relationship is between high suckling activity and prolonged lactational amenorrhea.[2,33-35]

## OVARIAN ACTIVITY POSTPARTUM

In non-breastfeeding women ovarian follicle development monitored by measurement of estrogen and progesterone and suppressed throughout pregnancy, resumes within two to three weeks postpartum and first ovulation can occur as early as 6 weeks postpartum.[4,36] During lactational amenorrhea ovarian activity is apparently suppressed in the majority of women since ovarian steroid secretion is minimal.[2,4,5,33,34,37] In some women transient increases in ovarian estrogen secretion occurs indicating the development of follicles, but ovulation rarely if ever occurs.[4,5,38-42] The pattern of ovarian follicle development during lactational amenorrhea has been clarified in a recent study[43] using serial ultrasound visualization of follicles during lactation (FIG. 2). Between 8 and 20 small follicles up to 8 mm in diameter equivalent to follicles present in the early- to mid-follicular phase of the normal menstrual cycle were present in most lactating women.[43] The appearance of these follicles was episodic, they persisted for a variable time and produced little or no steroid. In some women large follicles developed and produced estrogen but did not ovulate becoming luteinized unruptured or atretic follicle or developing into follicle cysts.[43] These observations profoundly alter our views on the mechanism controlling lactational infertility indicating that, as in some other species,[33,34] follicle growth is not completely inhibited. The cause of this follicle growth and variable pattern of steroid secretion will be discussed later in connection with the changes in the pattern of secretion of the gonadotrophins luteinizing hormone (LH) and follicle stimulating hormone (FSH).

As lactation progresses the possibility of ovulation occurring before first menses increases to 10 to 15% of women depending on the pattern of suckling. If suckling continues then a high proportion, up to 90%, of first ovulatory cycles are associated with short or inadequate luteal phases.[4,5,38-42] The proportions of normal, short or inadequate corpora lutea and the number of each that may occur before resumption of cycles with normal luteal function varies with each women and in each study. This relates to the variation in the suckling pattern of the individual baby and mother and the consequent effect on the secretion of gonadotrophins.

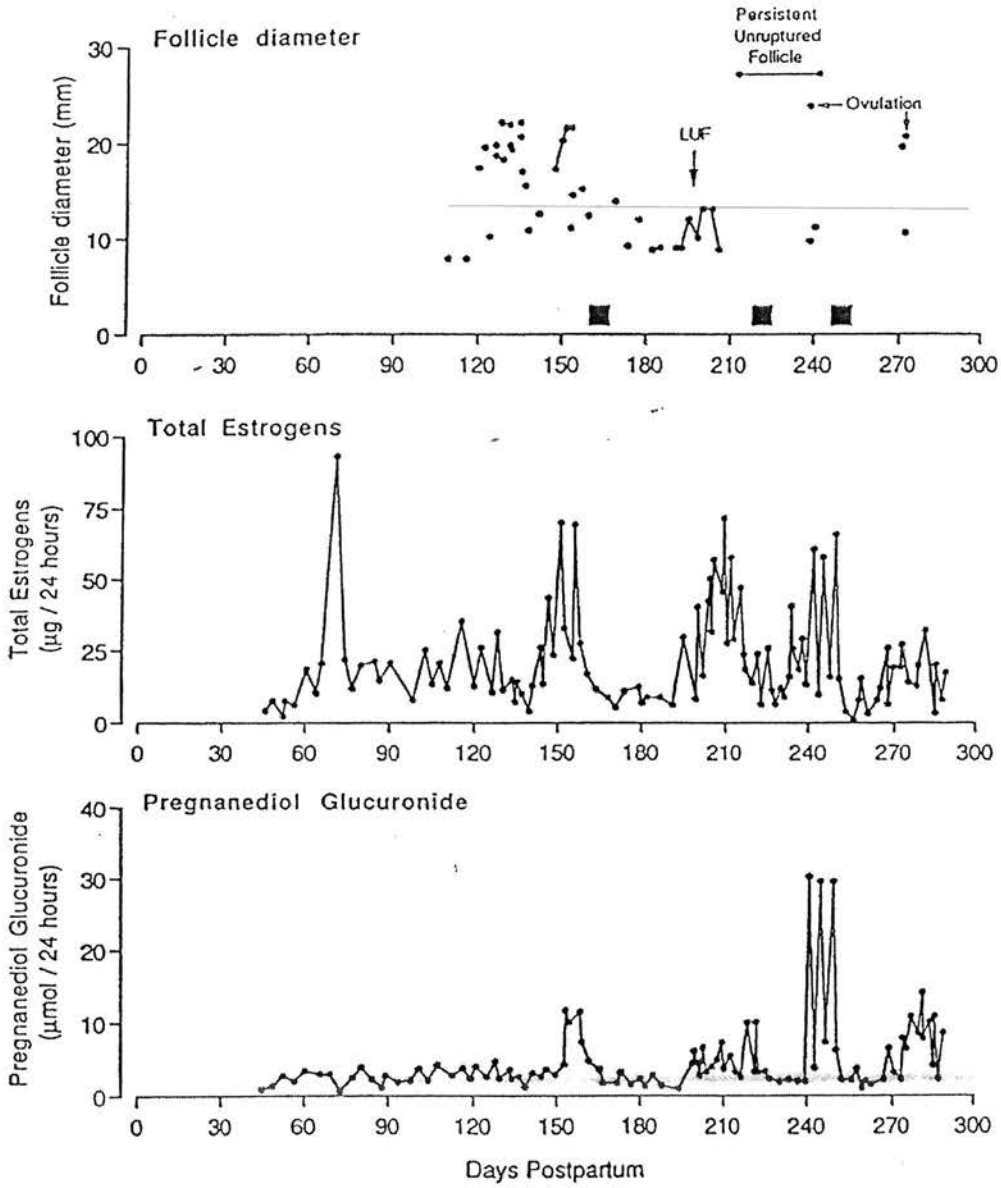


**FIGURE 2.** Changes in the number and size of follicles within the ovary, visualized by ultrasound in relation to changes in the pattern of ovarian total estrogen and pregnanediol glucuronide secretion in a breastfeeding women. Note that follicles up to 20mm in diameter were present in the ovary around day 120 postpartum but were steroidogenically relatively inactive secreting only small amounts of estrogen, compared to similar sized follicles at day 270 which were secreting normal amounts of estrogen and subsequently ovulated to form a normal corpus luteum. Around day 190 a follicle developed which did not ovulate, the luteinized unruptured follicle, LUF. Between days 210 and 240 a large follicle developed which did not ovulate, the persistent unruptured follicle. Menses (■) occurred after the decline in estrogen and progesterone secretion. (Redrawn from ref. 42.)

## GONADOTROPHINS

Follicle growth, ovulation and the formation of a viable corpus luteum able to support a pregnancy depends on the initial stimulation of follicle growth but not steroidogenesis by FSH followed by induction of steroid secretion by the pulsatile secretion of LH. The developing follicle secretes increasing amounts of estradiol which induces the preovulatory surge of LH when the follicle is mature at about 20mm in diameter, ovulation takes place and normal corpus luteum function, particularly the secretion of progesterone, is maintained by continued pulsatile secretion of LH. The pulsatile secretion of LH is caused by the pulsatile release of gonadotrophin releasing hormone (GnRH) from the hypothalamus.

During pregnancy pulsatile release of GnRH is inhibited so that at term pituitary content of LH is reduced to around 1% of normal.[44] Plasma concentrations of FSH in breastfeeding women increase to within normal early follicular phase levels by 4 to 8 weeks postpartum.[22,26,31,45,46] It is this increase in FSH which is probably responsible for the induction and continued production of the waves of follicle development observed by ultrasound during lactational amenorrhea. However, in the absence of adequate pulsatile LH stimulation these follicles will remain either steroidogenically inactive, or will produce only small amounts of estrogen.

Plasma concentrations of LH increase from undetectable levels around day 7 postpartum[26] to low normal by 3 to 4 weeks postpartum.[2,4,22,47] Recent studies monitoring the pulsatile patterns of LH secretion over 24h periods during the resumption of ovarian activity have now determined that pulsatile release of LH can occur by 4 weeks postpartum in breastfeeding women but that the frequency remains slow and variable (FIG. 3).[22] In another study very low amplitude LH pulses were released at a normal frequency[47] but the overall results indicate that LH pulses and, by implication pulsatile release of GnRH from the hypothalamus, is not completely inhibited throughout lactation. Thus when FSH stimulates follicle growth to occur pulsatile LH release may be occurring and this would allow the production of estradiol from a proportion of follicles. However, the amount of estradiol produced will vary considerably since the frequency of LH pulses is very variable.

As lactation progresses and suckling declines, the frequency of pulsatile LH secretion increases to near the frequency occurring in the normal follicular phase and sustained estradiol secretion will occur.[2,45] Although a normal increase in plasma estradiol may occur during breastfeeding this may not trigger the release of preovulatory surge of LH as would occur in the normal menstrual cycle. Is has been shown previously that in breastfeeding women the ability of estradiol to induce a preovulatory LH surge, positive feedback, is severely impaired.[48] Thus, although a follicle may grow to be of preovulatory size, and produce a normal estradiol signal, no LH surge would be induced and the follicle would become a luteinized unruptured follicle, atretic, or cystic, as observed by ultrasound.[43]

Only when suckling has reduced to the point where there is no longer an inhibition of both the normal pattern of pulsatile LH secretion and generation of a preovulatory LH surge will normal luteal function resume. This is apparently confirmed by our earlier observation that replacement of a normal pattern of GnRH release using a pulsatile infusion pump in fully breastfeeding amenorrheic women at 6 weeks postpartum resulted in development of normal estrogenic follicles observed by ultrasound, but inadequate luteal function occurred in the majority of these women related to a poor preovulatory LH surge.[49]

The link between the suckling stimulus activating nerve terminals in the nipple and the disruption of the pattern of release of GnRH from GnRH neurons in the hypothalamus remains unknown. Although high dopaminergic tone within the

hypothalamus associated with feedback effects of high plasma concentration of prolactin have been suggested as a possible mechanism, this does not appear to be the case. Treatment of breastfeeding women with the dopamine antagonist metoclopramide while causing a large release of prolactin, did not affect FSH or the pulsatile

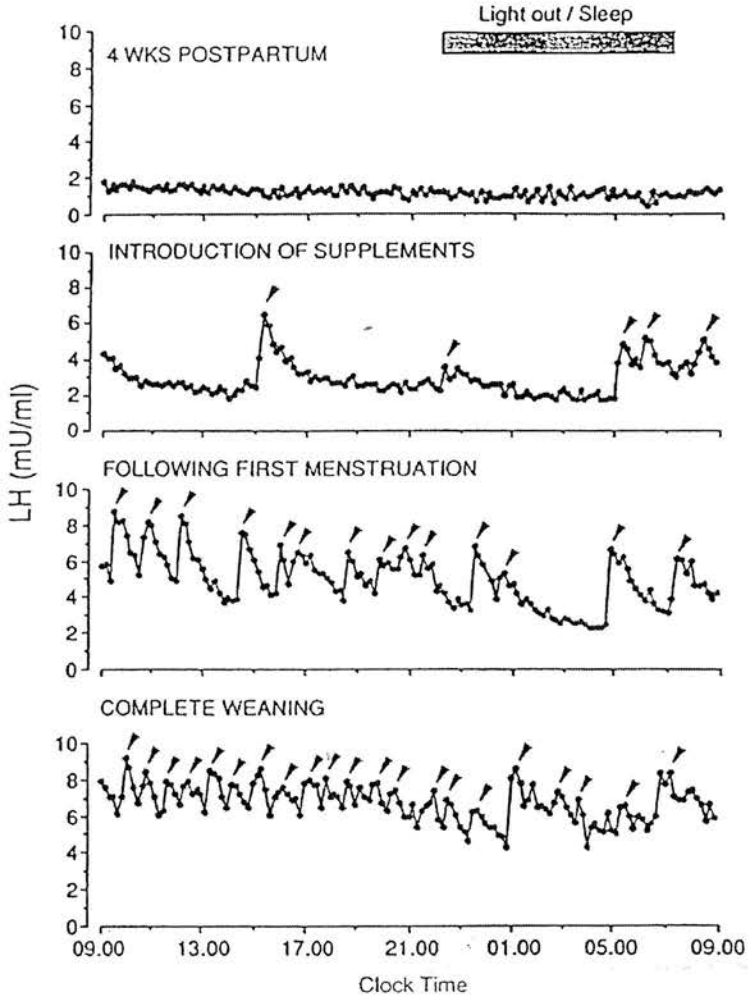


FIGURE 3. Progressive return of the pulsatile pattern of LH secretion over 24h periods at different stages in the return of normal ovarian activity in a breastfeeding women. No follicles were present at 4 weeks and at the introduction of supplements at 16 weeks only limited estradiol secretion was evident indicating the presence of a follicle. Follicle growth had resumed after first menses, but was associated with an inadequate corpus luteum, while normal menstrual cycles resumed after weaning when the pulsatile pattern of LH release was normal. ▶ indicates an LH pulse.

release of LH.[24] Thus an involvement of prolactin in suppressing GnRH output through altered hypothalamic dopaminergic activity does not appear to be tenable.

Opiates are known to suppress GnRH release and are associated with the decrease in GnRH pulse frequency caused by progesterone during the luteal phase of the

menstrual cycle.[50,51] There is conflicting evidence for a role of opiates in suckling-induced inhibition of GnRH release in other species[34] and no evidence for a role in the lactating monkey.[28] Similarly, there is no evidence in breastfeeding women to support a role for opiates in suckling-induced suppression of GnRH release.[24,26]

## SUMMARY

Breastfeeding delays the resumption of normal ovarian cycles by disrupting the pattern of pulsatile release of GnRH from the hypothalamus and hence LH from the pituitary. The plasma concentrations of FSH during lactation are sufficient to induce follicle growth, but the inadequate pulsatile LH signal results in a reduced estradiol production by these follicles. When follicle growth and estradiol secretion does increase to normal, the suckling stimulus prevents the generation of a normal preovulatory LH surge and follicles either fail to rupture, or become atretic or cystic. Only when the suckling stimulus declines sufficiently to allow generation of a normal preovulatory LH surge to occur will ovulation take place with the formation of a corpus luteum of variable normality. Thus suckling delays the resumption of normal ovarian cyclicity by disrupting but not totally inhibiting, the normal pattern of release of GnRH by the hypothalamus.

The mechanism of suckling-induced disruption of GnRH release remains unknown. It does not appear to involve prolactin, dopamine or opiates although a combination of these factors might be involved. Prolactin is the major hormone responsible for milk production and is present in sufficient quantities in almost all women to allow the establishment of normal lactation. Oxytocin is essential for milk let down and is susceptible to inhibition of release by stress. The successful initiation of lactation which would lead to the potential of utilizing breastfeeding as contraceptive may require more attention to be paid to the establishment of non-stress release of oxytocin.

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# Effect of antagonists of dopamine and opiates on the basal and GnRH-induced secretion of luteinizing hormone, follicle stimulating hormone and prolactin during lactational amenorrhoea in breastfeeding women

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**The role of dopamine and opiates in the suckling-induced suppression of gonadotrophin secretion and prolactin release was investigated during lactational amenorrhoea in fully breastfeeding women at 12 weeks post-partum. A total of 26 women, 20 using non-steroidal methods of contraception and six using the progestogen-only pill, Noriday (POP), breast-fed their babies on demand at a frequency of 3.6 ± 0.2 suckling episodes during the 8 h study period while blood samples were collected at 10-min intervals. Five hours after the start of sampling six women were given the dopamine antagonist metoclopramide (10 mg, i.m.) while four women received saline. In a second experiment, six women using non-steroidal contraception and three women on the POP received an i.v. infusion of the opiate antagonist naloxone (1.6 mg/h) for 2 h, while four women using non-steroidal contraception and three women on the POP were infused with saline. Two hours after the i.m. injection or start of infusion all women were given an i.v. injection of 10 μg gonadotrophin releasing hormone (GnRH) and samples were collected for a further 1 h. All samples were assayed for luteinizing hormone (LH), follicle stimulating hormone (FSH) and prolactin. Plasma concentrations of oestradiol were <60 pmol/l in all women and they remained amenorrhoeic for at least 10 weeks after the study. Pulsatile release of LH was only observed over the 5 h pre-treatment period in 10 of the 20 non-steroid taking women (1–3 pulses/5 h), and in one of the six women (1 pulse/5 h) on POP. Treatment with metoclopramide caused a substantial (29-fold) increase in prolactin over baseline, 7.4 times the maximum released in response to suckling. There was no effect of metoclopramide on the pattern of release of LH or FSH or the response to GnRH. Infusion of naloxone in women using either non-steroidal contraceptives or progestogen-only pill did not affect prolactin release. Naloxone infusion did not affect LH or FSH in women using non-steroidal contraceptives, but caused a small but significant ($P < 0.05$) increase in both LH and FSH in women taking the progestogen-only pill. There was a significantly greater release of LH and FSH after GnRH in all women after naloxone infusion. These results in breastfeeding women during lactational amenorrhoea confirmed that suckling suppresses the pulsatile release of LH but not through a dopaminergic pathway, showed that prolactin remains under dopaminergic control during human lactation, but suckling does not appear to affect prolactin secretion via an opiate pathway and indicated only a minor, if any, role for opiates in the suckling-induced suppression of GnRH/gonadotrophin secretion but a potential, previously unreported, effect of opiates in reducing pituitary responsiveness to GnRH.**

*Key words*: dopamine/lactational amenorrhoea/opiates/prolactin/pulsatile LH/FSH

## Introduction

The suppression of ovarian activity in breastfeeding women is associated with an alteration in the pulsatile pattern of secretion of luteinizing hormone (LH) (Glasier *et al.*, 1984; Tay *et al.*, 1992). Since there is clear evidence that pulsatile LH release occurs in response to the pulsatile secretion of gonadotrophin releasing hormone (GnRH) from the hypothalamus (Clarke and Cummins, 1982) it is assumed that the suckling stimulus inhibits the release of hypothalamic GnRH. It is not known how this effect may be mediated.

In all species studied, lactation is associated with increased prolactin (McNeilly, 1988). Because of the close association between raised prolactin levels and the suppression of ovarian activity post-partum in the human (McNeilly, 1988; Glasier and McNeilly, 1990) together with the knowledge that disturbances of LH secretion are associated with pathological hyperprolactinaemic amenorrhoea, it has been suggested that prolactin may play a role in suppressing gonadotrophin secretion. High levels of prolactin increase dopamine turnover in the hypothalamus and in some species (see e.g. Adler, 1986; McNeilly, 1988) there is evidence that increased release of dopamine into the hypothalamo–pituitary–portal system results in decreased release of LH. Thus it has been suggested that increased dopamine tone may inhibit the GnRH pulse generator, thereby inhibiting the normal pulsatile pattern of LH secretion.

Changes in endogenous opioid peptides and alterations in dopamine turnover are both known to modify the secretory activity of the hypothalamic neuroendocrine neurones. Opioids may play a role in the control of the human ovarian cycle (Quigley and Yen, 1980; Ferin *et al.*, 1984) and abnormalities of opioid tone may be involved in disturbances of the menstrual cycle (Quigley and Yen, 1980; Grossman *et al.*, 1982). Moreover, there is some evidence in species other than the human that

suckling-induced release of opioids may be the principal mediator of the suppression of LH release during lactation. Both the concentration and secretion rate of $\beta$-endorphin in hypothalamo–pituitary–portal blood increased in response to suckling episodes in ewes (Gordon *et al.*, 1987) while treatment of both suckling rats (Sirinathsinghi and Martini, 1984) and sows (Mattioli *et al.*, 1986) with the opioid antagonist naloxone resulted in a significant increase in LH concentrations. In the human, treatment of non-breastfeeding women with naloxone between 13 and 25 days after delivery resulted in increased concentrations of both LH and FSH (Ishizuka *et al.*, 1984) and it has been suggested that the hypogonadotrophism of the puerperium is due in part to increased opioid inhibition of GnRH secretion.

In order to determine whether a suckling-induced increase in either opioid or dopamine tone may be involved in the suppression of pulsatile LH release in the human we have investigated the effects of the dopamine antagonist metoclopramide and of the opioid antagonist naloxone on the secretion of LH, FSH and prolactin during lactational amenorrhoea in breastfeeding women.

## Materials and methods

### *Subjects and treatments*

Twenty-six women who intended to breastfeed their infants without supplementing for at least 3 months were recruited from the postnatal wards of the Simpson Memorial Maternity Pavilion (SMMP) in Edinburgh. The women were in good health and had a history of regular menstrual cycles prior to conceiving. Six of the women who were specifically recruited to investigate the influence of progestogen began taking the progestogen-only pill (Noriday, norethisterone 0.35 mg/day) at 6 weeks post-partum while 20 used no form of steroidal contraception but relied on non-steroidal methods. All 26 women were studied at 12 weeks post-partum while fully breastfeeding and amenorrhoeic. Written informed consent was obtained and the study was approved by the local ethical committee.

On the day of treatment with either the dopamine antagonist metoclopramide, or opiate antagonist naloxone, the women were admitted to the research ward of the SMMP at 0830 h. An intravenous cannula was inserted into a forearm vein and kept patent with heparinized saline. From 0900 h 5 ml of venous blood was collected every 10 min for 5 h in order to establish the baseline pattern of secretion of gonadotrophins. After 5 h (at 1400 h) the following treatment groups were established. Group A received a single i.v. injection of metoclopramide 10 mg: (i) non-steroidal contraception, $n = 6$. Group B received a single i.v. injection of normal saline: (i) non-steroidal contraception, $n = 4$. Group C received an i.v. infusion of normal saline for 2 h: (i) non-steroidal contraception, $n = 4$; (ii) POP, $n = 3$. Group D received an i.v. infusion of naloxone 1.6 mg/h for 2 h: (i) non-steroidal contraception, $n = 6$; (ii) POP, $n = 3$.

The administered dose of metoclopramide has been used in breastfeeding women and shown to cause maximum release of prolactin (Guzman *et al.*, 1979), while the infusion rate of naloxone has been shown to induce an increase in LH and FSH in non-breastfeeding women (Ishizuka *et al.*, 1984), and neutralize the effect of morphine (Grossman *et al.*, 1982). Women were allocated at random to groups A, B, Ci and Di, and the six women on the POP were allocated randomly to either naloxone or saline treatments. Since there was no significant effect of either a single i.v. injection or an i.v. infusion, the control group effectively consisted of eight women comprising the four women of group B and the four women of group Ci, although for analysis their results were not combined.

Blood sampling was continued every 10 min for 2 h until 1600 h when all 26 women were given an i.v. injection of 10 $\mu$g GnRH (Gonadorelin, Ayerst, Andover, UK). Blood samples were collected every 10 min for another hour after GnRH administration until 1700 h when the cannula was removed and the women allowed home. Plasma was separated and stored at −20°C until later assayed for LH, FSH and prolactin in batches. Serum oestradiol was measured in the first sample collected from each woman.

Throughout the day women were allowed to breastfeed their babies on demand at a mean frequency of 3.6 ± 0.2 and 1.4 ± 0.2 feeds in the total 8 h and the 2 h treatment period, respectively. Regular meals were provided and no restriction on movement was imposed.

### *Hormone assays*

Plasma concentrations of LH and FSH were measured by radioimmunoassay as described previously (Glasier *et al.*, 1984; Tay *et al.*, 1992) while plasma prolactin was measured in a two-site immunoradiometric assay (NETRIA, St Bartholomew's Hospital, London; Wu *et al.*, 1990). The intra- and inter-assay coefficients of variation were <8% and <11% respectively for LH, FSH and prolactin. Plasma oestradiol concentrations were measured by specific radioimmunoassay following diethyl ether extraction of serum as described previously (Glasier *et al.*, 1988). The intra- and inter-assay coefficients of variation were 4 and 15.8%, respectively.

### *Statistical analysis*

The data are presented as the mean ± SEM except where otherwise stated. Comparisons between mean hormonal concentrations and LH pulse frequency were performed using analysis of variance (ANOVA) on log-transformed data. Significant hormone pulses were identified using the Munro pulse analysis programme (Zaristow Software, Haddington, Scotland EH14 4PD) as described previously (Tay *et al.*, 1992).

## Results

All women were amenorrhoeic at the time of the studies and remained amenorrhoeic for at least 10 weeks afterwards. The plasma concentration of oestradiol at the time of sampling was <60 pmol/l in all women indicating an absence of ovarian activity.

### *Effect of metoclopramide*

Mean basal concentrations of LH, FSH and prolactin, mean concentrations following the i.v. bolus injection of either 10 mg metoclopramide or normal saline and following 10 $\mu$g GnRH i.v. for women in groups A and B are shown in Table I. The changes

in mean plasma concentrations of LH and FSH throughout the total sampling period for all women and the prolactin response for two individual women, one treated with metoclopramide and one control subject, are shown in Figure 1. One subject had surprisingly high concentrations of both LH and FSH (mean basal levels 12.0 ± 0.7 mU/l and 37.0 ± 0.6 mU/l respectively) throughout the sampling period and a response to exogenous GnRH stimulation at least three times higher than that of the other women in the study. The plasma oestradiol of that subject at the time of sampling was <60 pmol/l and she remained amenorrhoeic for a further 13 weeks, subsequently resuming regular menstrual cycles. This subject's results were included in the analysis.

In the 5 h prior to the injection of metoclopramide, five women had no statistically significant pulses of LH secretion while in the other five women a single pulse of LH was identified. There

**Table I.** Changes in the mean (± SEM) plasma concentrations of LH, FSH and prolactin in breastfeeding women with lactational amenorrhoea, 12 weeks post-partum during the 5 h before (basal), the 2 h after i.v. injection of 10 mg metoclopramide ($n$ = 6) or saline ($n$ = 4) and during the 1 h after i.v. injection of 10 μg GnRH

| Hormone | Treatment | Hormone concentration | |
|---|---|---|---|
| | | Saline | Metoclopramide |
| LH (U/l) | Basal | 3.42 ± 0.50 | 3.36 ± 0.84 |
| | Saline or metoclopramide | 2.71 ± 0.42 | 2.90 ± 0.75 |
| | GnRH | 24.08 ± 4.03 | 29.32 ± 11.50 |
| FSH (U/l) | Basal | 3.75 ± 0.40 | 4.08 ± 0.84 |
| | Saline or metoclopramide | 3.24 ± 0.32 | 3.64 ± 0.65 |
| | GnRH | 10.76 ± 2.05 | 10.77 ± 1.68 |
| Prolactin (mIU/l) | Basal | 1345 ± 140 | 1489 ± 1318 |
| | Saline or metoclopramide | 2140 ± 370 | 8760 ± 1157** |
| | GnRH | 2475 ± 450 | 5516 ± 753 |

**$P$ < 0.05 compared with saline control (ANOVA).
LH = luteinizing hormone; FSH = follicle stimulating hormone; GnRH = gonadotrophin releasing hormone.

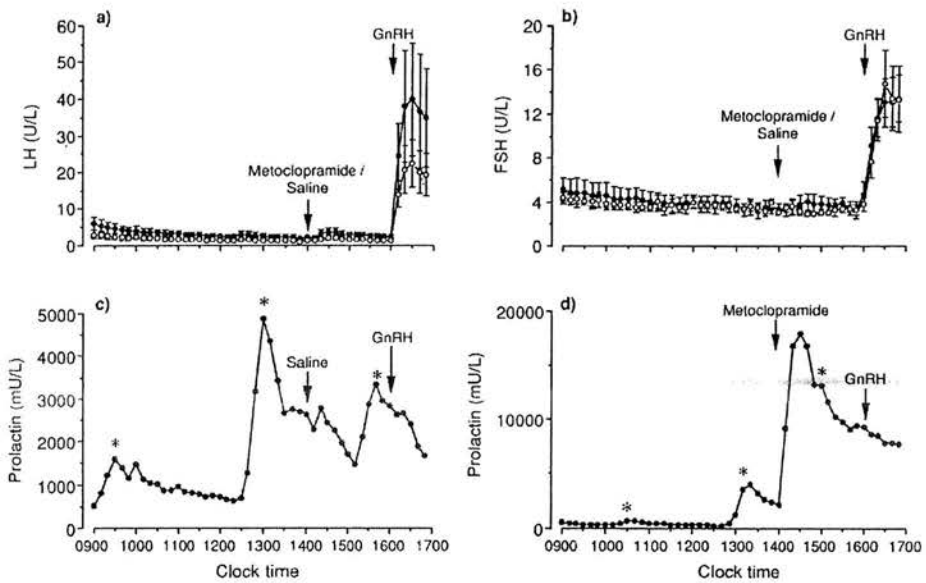


**Fig. 1.** Plasma concentrations (mean ± SEM) of (a) luteinizing hormone (LH) and (b) follicle stimulating hormone (FSH) in breastfeeding women with lactational amenorrhoea, 12 weeks post-partum during the 5 h before, 2 h after the i.v. injection of metoclopramide (●; $n$ = 6) or saline (○; $n$ = 4), and after the i.v. injection of a 10 μg bolus of GnRH. The profiles of prolactin in two individual women treated with saline (c) or metoclopramide (d) are also shown. *Indicates when suckling occurred on demand.

were no differences in basal plasma concentrations of LH, FSH or prolactin between women treated with metoclopramide or with saline prior to the injection of metoclopramide (Table I). Suckling occurred 2.1 ± 0.2 (SEM) times during the 5 h before treatment and induced a significant ($P < 0.001$) 9.6 ± 4.6-fold (SEM; $n = 19$ suckling episodes) increase in prolactin after every suckling episode with plasma prolactin concentrations increasing from an immediate pre-suckling concentration of 694 ± 160 mU/l to a maximum of 2542 ± 435 mU/l.

Administration of metoclopramide caused an immediate, highly significant ($P < 0.001$), increase in plasma prolactin to maximum concentrations of 14 954 ± 1936 mU/l (Table I), a response 29.1 ± 8.3-fold higher than basal prolactin and 7.4 ± 2.1-fold higher than maximum plasma concentrations of prolactin after suckling. There was no correlation between the basal concentration of prolactin, the response to suckling or the response to metoclopramide. Despite the massive increase in prolactin concentrations immediately following metoclopramide there was no change in the concentration or pattern of secretion of either LH or FSH. There were no significant differences between treated women and controls in either the LH or FSH response to exogenous GnRH (Table I, Figure 1).

### *Effect of naloxone*

Ten breastfeeding women using non-steroidal methods of contraception were infused i.v. with either naloxone 1.6 mg/h ($n = 6$) or normal saline ($n = 4$). Mean basal concentrations of LH, FSH and prolactin together with concentrations in response to the infusion of naloxone and exogenous GnRH administration are shown in Table II. Mean concentrations of gonadotrophins during the study for both groups of women are shown in Figure 2. Six women, three in each group had no statistically significant pulses of LH secretion in the 5 h prior to the onset of infusion while four women (three naloxone-treated and one control) did show a pulsatile pattern of secretion although pulse frequency was low (1.8 ± 0.34 pulses per 5 h). Because of the possible influence of the basal levels of LH and FSH on the subsequent response to both naloxone and GnRH, the results from the naloxone group were analysed together (Table II) and as those with and those without LH pulses (Figure 2a,c).

The infusion of naloxone did not significantly affect either the concentration or the pattern of secretion of either LH or FSH in the naloxone-treated women compared with the controls (Table II; Figure 2) regardless of the basal levels of LH or FSH. Although there was an increase in both LH and FSH during the naloxone infusion in those women with LH pulses, LH and FSH levels during naloxone infusion were not significantly different from the overall mean level of FSH and LH before infusion (Figure 2a,c). There was no increase in either LH or FSH during naloxone infusion in the women without LH pulses (Figure 2a,c). Suckling occurred on demand throughout the infusion of naloxone or saline at a frequency of 1.7 ± 0.3 and 1.5 ± 0.2 episodes respectively. We did not attempt to fix the time of suckling to the time of infusion. Although this made the prolactin data more difficult to interpret there was no change in prolactin during the infusion of naloxone (Table II; Figure 2). The concentrations of both LH and FSH following GnRH were significantly (LH: $P < 0.01$; FSH: $P < 0.05$) higher in women who had been infused with naloxone compared with controls regardless of the basal level of LH and FSH either before or during the naloxone infusion (Table II; Figure 2a,c).

Of the six women using POP contraception a pulsatile pattern of LH secretion was identified in only one with only a single pulse in the 5 h sampling period. Mean concentrations of gonadotrophins and prolactin during the sampling period are shown in Table III. Mean basal concentrations of prolactin and FSH were not different from those in women using non-steroidal methods of contraception. Mean basal concentrations of LH tended to be lower in women using the POP compared with women not exposed to exogenous progestogens (3.3 ± 0.4 versus 7.7 ± 1.7 U/l) although this difference was not statistically significant. Naloxone infusion resulted in a significant ($P < 0.05$) increase in both LH and FSH concentrations compared to saline infusion and within the group when compared with baseline levels but did not significantly affect prolactin levels (Table III). Concentrations of both LH and FSH increased significantly over baseline levels ($P < 0.05$) in response to GnRH stimulation and the plasma concentration of LH but not FSH after GnRH was significantly ($P < 0.05$) higher in the group treated with naloxone (Table III). The magnitude of the

**Table II.** Changes in the mean (±SEM) plasma concentrations of LH, FSH and prolactin during 5 h before (basal), the 2 h during i.v. infusion of naloxone (1.6 mg/h; $n = 6$) or saline ($n = 4$) and during the 1 h after i.v. injection of 10 μg of GnRH

| Hormone | Treatment | Hormone concentration | |
|---|---|---|---|
| | | Saline | Naloxone |
| LH (U/l) | Basal | 5.58 ± 1.38 | 8.96 ± 2.55 |
| | Saline or naloxone | 5.48 ± 1.37 | 12.5 ± 4.46 |
| | GnRH | 24.17 ± 3.39 | 47.14 ± 5.21** |
| FSH (U/l) | Basal | 4.89 ± 1.35 | 7.29 ± 1.40 |
| | Saline or naloxone | 4.48 ± 1.37 | 8.37 ± 1.92 |
| | GnRH | 11.49 ± 0.12 | 18.54 ± 2.21** |
| Prolactin (mIU/l) | Basal | 1357 ± 448 | 857 ± 231 |
| | Saline or naloxone | 1643 ± 623 | 1509 ± 261 |
| | GnRH | 1938 ± 680 | 1777 ± 538 |

*$P < 0.05$. **$P < 0.01$ compared with saline control.

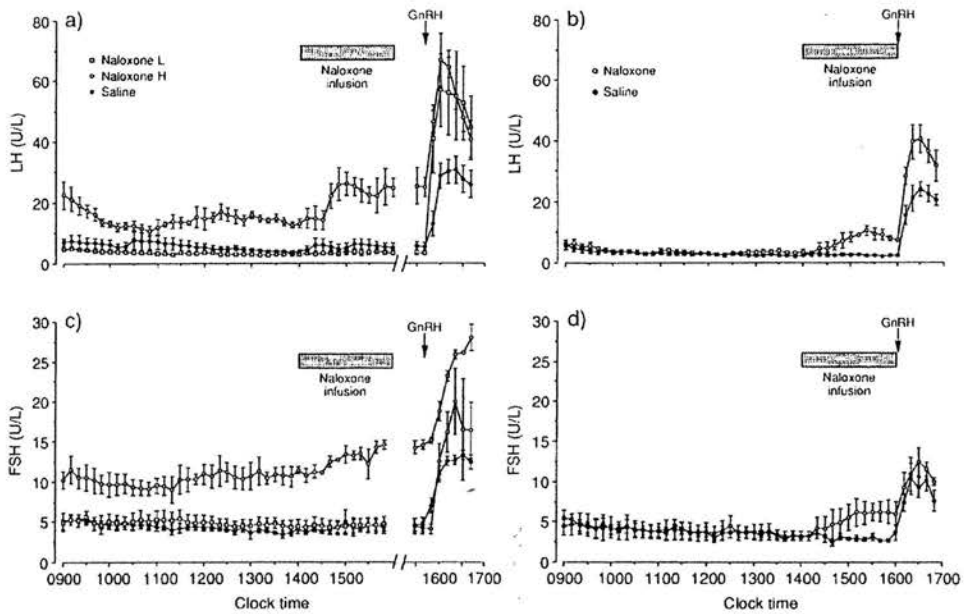


**Fig. 2.** Plasma concentrations (mean ± SEM) of luteinizing hormone (LH) (**a,b**) and follicle stimulating hormone (FSH) (**c,d**) during the 5 h before, 2 h after i.v. infusion of naloxone (○,□: 1.6 mg/h) or saline (●), and after i.v. injection of a 10 μg bolus of GnRH in breastfeeding women with lactational amenorrhoea, 12 weeks post-partum, using either non-steroidal contraception (**a,c**: $n = 6$, naloxone; $n = 4$, saline), or the progestogen-only-pill norethisterone (POP; **b,d**: $n = 3$, naloxone; $n = 3$, saline). In the non-POP group 3 women (○) had, and 3 women (□) did not have, a pulsatile pattern of LH release in the 5 h period before naloxone infusion.

**Table III.** Changes in the mean (±SEM) plasma concentrations of LH, FSH and prolactin in breastfeeding women with lactational amenorrhoea, 12 weeks post-partum, taking the progestogen only contraceptive, during the 5 h before (basal), the 2 h after i.v. infusion of naloxone (1.6 mg/h, $n = 3$) or saline ($n = 3$) and during the 1 h after i.v. injection of 10 μg GnRH

| Hormone | Treatment | Hormone concentration | |
|---|---|---|---|
| | | Saline | Naloxone |
| LH (U/l) | Basal | 3.10 ± 0.52 | 3.74 ± 0.78 |
| | Saline or naloxone | 2.50 ± 0.44 | 6.85 ± 0.95* |
| | GnRH | 17.47 ± 2.26 | 30.42 ± 3.34* |
| FSH (U/l) | Basal | 3.99 ± 0.65 | 3.99 ± 1.03 |
| | Saline or naloxone | 3.05 ± 0.18 | 5.12 ± 1.33* |
| | GnRH | 8.10 ± 1.24 | 10.08 ± 1.35 |
| Prolactin (mIU/l) | Basal | 610 ± 120 | 1450 ± 170 |
| | Saline or naloxone | 1010 ± 260 | 2020 ± 250 |
| | GnRH | 930 ± 390 | 2180 ± 300 |

*$P < 0.05$ compared with saline control.

increase in LH, but not FSH, following GnRH stimulation was lower in women using POP than women using non-steroidal methods of contraception treated with saline, but this difference was not significant. In women using non-steroidal methods of contraception the prolactin response to suckling before infusion of naloxone or metoclopramide was not significantly different from that in women taking the POP (non-steroidal method: 1289 ± 183 U/l; POP: 1096 ± 219 U/l).

## Discussion

In this study we have sought to determine the role of dopamine and opiates in the suckling-induced inhibition of LH and FSH secretion known to underlie the suppression of ovarian activity during lactational amenorrhoea (McNeilly, 1988). As in our previous studies (Glasier *et al.*, 1984; Tay *et al.*, 1992) using the same radioimmunoassay reagents, we confirmed that LH

pulse frequency was low at 12 weeks post-partum, when ovarian activity assessed by the low levels of plasma oestradiol was suppressed (data not shown). In contrast, a previous report suggested that a normal frequency of LH pulsatile release had resumed in most breastfeeding women by 3 months of lactation, although the amplitude of these pulses may be reduced (Nunley *et al.*, 1991). We can offer no explanation for this difference in pattern of LH release in the two studies except the difference in assay reagents used. We also showed in the present study that pulsatile release was further suppressed in women taking a POP contraceptive, but that in all women, a bolus injection of GnRH caused a substantial release of both LH and FSH, confirming that the assay method used in the present study would detect LH pulses if present.

The short-loop feedback effect of prolactin causes an increase in dopaminergic activity in the hypothalamus of the rat (Selmanoff, 1985). This finding together with the suppressive effects of dopamine on LH release in certain situations in women (Ferran *et al.*, 1981), and the resumption of normal LH secretion and ovarian activity in hyperprolactinaemic patients when treated with dopaminergic drugs to suppress prolactin (Thorner *et al.*, 1974) have suggested that the high plasma concentrations of prolactin associated with lactational amenorrhoea were causal in suppressing GnRH release, via raised hypothalamic dopaminergic activity. However, this theory has been questioned (McNeilly, 1987) but has not been tested in breastfeeding women before. Indeed, there is little evidence to support the theory of prolactin-induced increased hypothalamic dopaminergic activity, since, even in lactating rats, hypothalamic dopaminergic activity is reduced, and the ability of prolactin to increase hypothalamic dopamine is suppressed (Demarest *et al.*, 1983; Selmanoff and Wise, 1981).

Our present study shows that blockade of dopamine receptors by the dopamine antagonist metoclopramide in breastfeeding women did not affect the pattern of LH or FSH secretion, or the pituitary response to GnRH. However, metoclopramide did result in a very large increase in plasma concentrations of prolactin, to levels several-fold higher than after any natural suckling episode. This implies that prolactin secretion during human lactation remains under dopaminergic inhibition and that suckling could increase prolactin release simply by reducing dopamine release from the hypothalamus since the time course of release was similar after suckling and metoclopramide. This does not exclude the possibility that suckling may release other factor(s) that would positively drive the release of prolactin as suggested by studies in the monkey (Frawley *et al.*, 1983). Nevertheless, the present results showing no effect of inhibition of dopamine and absence of effect of a very large increase in plasma concentrations of prolactin supports our contention that the suckling-induced inhibition of GnRH release is not directly related to prolactin (McNeilly, 1987, 1988; Tay *et al.*, 1992), a conclusion also reached in recent studies in the rat (Maeda *et al.*, 1991).

Studies in animals have suggested that suckling may suppress GnRH by increasing hypothalamic opiate tone (McNeilly, 1988; Rasmussen, 1991). Treatment of lactating rats (Sirinathsinghji and Martini, 1984), sows (Mattioli *et al.*, 1986) but not cows (Canfield and Butler, 1991) with opiate antagonists increases LH secretion while suckling causes an increase in $\beta$-endorphin concentration in the hypophyseal portal blood in lactating ewes (Gordon *et al.*, 1987). Infusion of naloxone at the same rate used in the present study (Lodico *et al.*, 1983) in non-breastfeeding women, resulted in an increase in LH and FSH which occurred from day 15 post-partum onwards, this increase in response coinciding with both an increase in response to GnRH and with an increase in ovarian steroids. Treatment with naltrexone in non-breastfeeding women on day 7 post-partum did not affect LH (Kremer *et al.*, 1991).

In the present study administration of an opioid antagonist had no statistically significant effect on gonadotrophin concentrations in breastfeeding women who were not taking steroids and were hypo-oestrogenic (oestradiol $< 60$ pmol/l) studied at 12 weeks post-partum regardless of their pattern of gonadotrophin secretion before naloxone infusion. This suggests that opiates are either not involved in, or make only a minor contribution to, the suckling-induced suppression of GnRH release in these women, a conclusion in agreement with recent results in the lactating monkey (Gordon *et al.*, 1992). In contrast, a significant although small increase in both LH and FSH occurred after naloxone treatment in the breastfeeding women who were taking the POP. In the normal menstrual cycle (Quigley and Yen, 1980) administration of naloxone increases LH concentrations in the late follicular and luteal phase but has no effect on the early follicular phase when circulating steroids are low. Our results suggest that opiates are either not, or only minimally involved in, the suckling-induced suppression of GnRH and hence LH and FSH release, but that a more significant inhibitory effect of opiate can be induced by steroids during lactation. Breastfeeding women are more sensitive to the negative feedback effects of oestradiol (Baird *et al.*, 1979; Glass *et al.*, 1981) and we have previously suggested that the disruption of the pulsatile pattern of LH and, by implication GnRH, is related to this suckling-induced, enhanced steroid inhibition of GnRH release (McNeilly, 1988). The present results suggest that the effect of steroids in lactation may involve increased opiate activity.

A surprising result was the enhanced release of both LH and FSH in response to GnRH after naloxone infusion, which occurred regardless of the basal levels of LH and FSH, and by implication GnRH input, before naloxone treatment. To our knowledge this has not been reported before in any circumstances. This increase in release presumably related to an increase in the sensitivity of the gonadotrophs in the pituitary to GnRH, induced by blockade of opiate receptors. This is a very surprising result since there is no evidence of opiate receptors on the pituitary gonadotrophs (Horton *et al.*, 1990) all effects of opiates apparently acting via the hypothalamus (Horton *et al.*, 1990; Rasmussen, 1991). At present we have no explanation for this finding. It does indicate a potential role for opiates, possibly $\beta$-endorphin of pituitary origin, having a direct effect on the pituitary gonadotrophs to reduce responsiveness to GnRH during lactation.

There was no effect of naloxone on the release of prolactin in the present study. This confirms previous studies in which naloxone failed to affect basal and breast-pump induced prolactin

release in the first 2–3 days post-partum (Lodico *et al.*, 1983), and the response to suckling between 55 and 129 days post-partum (Cholst *et al.*, 1984). Thus, although opiates will increase prolactin release in non-lactating women (e.g. Tolis *et al.*, 1975) and are involved in maintaining prolactin secretion during lactation in the monkey (Gordon *et al.*, 1992), there is no evidence to support a role for opiates in mediating the prolactin response to suckling in breastfeeding women. In addition we found no evidence that the progestogen norethisterone enhanced the release of prolactin in response to suckling. This contrasts to a recent report in which suckling induced a significantly greater release of prolactin in women using a vaginal ring releasing progesterone (Diaz *et al.*, 1991).

In summary, the present study in breastfeeding women during lactational amenorrhoea confirmed that suckling suppresses the pulsatile release of LH but not through a dopaminergic pathway; showed that prolactin remains under dopaminergic control during human lactation, but suckling does not appear to affect prolactin secretion via an opiate pathway; and indicated only a minor, if any, role for opiates in the suckling-induced suppression of GnRH/gonadotrophin secretion but a potential, previously unreported, effect of opiates in reducing pituitary responsiveness to GnRH.

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# 10

# Physiology of lactation

ANNA GLASIER
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## ANATOMY AND DEVELOPMENT OF THE BREAST

### Anatomy

The adult female breast is divided into 15–20 lobes by fibrous septa. Each lobe can be considered as a separate gland within the fatty substance of the breast itself. Glandular tissue within each of the lobes drains towards the nipple through a lactiferous duct which dilates slightly within the nipple to form the lactiferous sinus. Lobes are subdivided into discrete lobules each with its own excretory duct—the interlobular duct. The basic glandular secretory units of the breast are the alveoli which cluster around the mammary ductules and produce milk. Surrounding each alveolar unit is a network of specialized myoepithelial or 'basket' cells responsible for ejection of milk from the alveoli and alveolar ducts.

### Development

Development of the mammary gland in the human begins at about 8 weeks of fetal life with the formation of mammary buds consisting of a ball of epithelial cells extending into the underlying mesenchyme. During the second trimester each bud sprouts 15–20 branches which form rudimentary mammary ducts (Neville, 1983). In the third trimester of pregnancy high concentrations of fetal prolactin stimulate terminal differentiation of the ductal cells. Milk secretion by the infant following delivery is not uncommon. After a period of quiescence during childhood the increase in ovarian steroid secretion at puberty stimulates ductal development and the deposition of adipose tissue within the gland (Figure 1). The human is the only animal in which significant growth of the mammary gland occurs in the absence of pregnancy. Pubertal growth will not occur, however, in the absence of ovarian oestrogen stimulation (Baron, 1958). Other factors such as epidermal growth factor (EGF) or an as yet unidentified mammary growth factor may also be required, indeed it may be that it is through such factors that oestrogen has its action. In animals (Cowie et al, 1966) hypophysectomy inhibits the development of the mammary gland in the presence

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Figure 1. Development and regression of the ductal and alveolar system in the breast: (A) prepubertal, (B) in a cycling nulligravida, (C) primigravida at 8 weeks gestation, (D) 3 weeks postpartum 48 h after last suckling episode, (E) 5 years after last delivery. Modified from Dabelow 1957.

of oestrogen and progesterone, suggesting that a pituitary hormone such as prolactin may also be involved.

### Changes in pregnancy

In the non-pregnant state in the adult woman connective tissue and adipose tissue predominate and glandular tissue is scanty. In pregnancy the human breast undergoes marked changes. In the first trimester both ductal and secretory elements undergo hyperplasia which results in a rapid increase in the number of alveoli. In later pregnancy, development is characterized by alveolar cell hypertrophy and there is a marked decrease in the relative amount of adipose and fibrous tissue. Within 48 h of delivery the alveoli become distended with milk following intense secretory activity. With weaning and cessation of breastfeeding regression of the gland occurs rapidly, remaining milk is resorbed and there is a steady decrease in glandular tissue and increasing predominance of connective tissue. Many of



the alveoli persist, however, until the next pregnancy so that the tissue does not resemble the prepubertal breast histologically.

### Endocrine control of breast development

The endocrine control of mammogenesis has been widely investigated in some animal species including the rat in which a complex interaction between ovarian and adrenal steroids, growth hormone and prolactin is required to enable the production of milk. In the human a fair amount of preparation occurs without pregnancy and in the non-pregnant state adult breast tissue is sufficiently differentiated to begin secreting milk after only 14 days exposure to high concentrations of oestrogens (Tyson et al, 1976). Milk production does indeed occur in some women at mid-cycle following follicular phase oestrogen stimulation and when in the normal cycle prolactin levels are normally slightly elevated. Milk production may persist until menstruation.

Sensitivity of the breast to ovarian steroids persists throughout the reproductive years. In vitro cultures of breast tissue respond to oestrogen with ductal development and to progesterone with alveolar proliferation (McNeilly, 1977). Changes in mitotic activity in the breast lobules can be seen in relation to fluctuations in steroid hormones throughout the menstrual cycle with an increase in cell proliferation in the second half of the cycle (Going et al, 1988). Fluctuations related to the menstrual cycle have also been described in secretory products from the breast including IgA, secretory component and β-lactalbumin. However, no clear relationship between cell proliferation and secretory activity has yet been described and the increase in mitotic index in the second half of the cycle is demonstrable in women on the combined oral contraceptive. Premenstrual mastalgia is thought to be due to hyperaemia and tissue oedema, however, rather than to marked cell proliferation, and indeed this is reflected by a significant increase in breast volume in the second half of the cycle (Milligan et al, 1975).

## LACTATION

### Initiation of milk secretion

While milk is secreted into the alveoli from the second trimester of pregnancy in the human the onset of copious secretion occurs only gradually after the first few days following parturition—later than in most other mammals. It is now clear that lactogenesis is triggered by a fall in progesterone concentrations in the presence of mammary development and prolactin concentrations sufficient to allow milk secretion (Figure 2). After delivery of the placenta, placental lactogen disappears within hours; progesterone and oestrogen fall over 5–6 days and prolactin over 14–21 days unless suckling occurs. Progesterone is a specific inhibitory factor to the onset of milk production. It does not inhibit established lactation, however, perhaps because actively

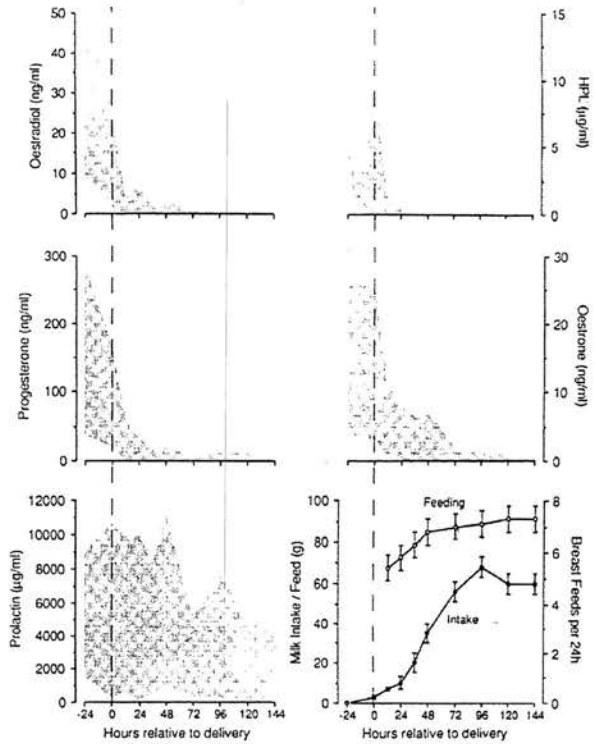


**Figure 2.** Range of serum oestradiol, progesterone, prolactin, and human placental lactogen (HPL) and urinary oestrone concentrations before and after delivery in a group of breast-feeding women. Also shown is the mean suckling frequency and mean milk intake by the infant during the first week postpartum.

lactating tissues do not contain progesterone receptors. That prolactin is necessary for the onset and continuation of lactation is demonstrated by the fact that a specific dopamine agonist such as bromocriptine inhibits prolactin secretion and prevents milk production (Rolland and Schellekens, 1973).

### Maintenance of milk secretion

Once lactation is established, the continued production of milk requires prolactin (Figure 3). In all species so far studied, prolactin concentrations



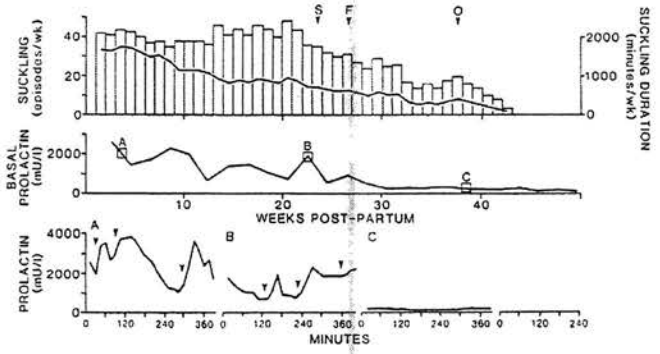


**Figure 3.** Prolactin concentrations in relation to suckling activity and time postpartum. In the top figure the number (bars) and duration (line) of suckling episodes each week are shown; S = introduction of solids, F = onset of ovarian activity, O = first ovulation. In the middle figure fortnightly prolactin concentrations are seen to fall in parallel with the decline in suckling activity. The acute response of prolactin to suckling, with samples taken every 15 min, at (A) 4 weeks, (B) 20 weeks, and (C) 38 weeks postpartum, is shown in the bottom figure. From Glasier et al (1984b).

are raised during lactation and prolactin is released in response to the suckling stimulus. In the human the prolactin response to suckling is greatest in the early weeks of lactation and declines with time postpartum. In general the onset of suckling results in an increase in serum prolactin concentrations almost immediately, followed by a fall over the subsequent hour such that 2 h after a suckling episode levels have fallen to baseline. Clearly, if suckling episodes occur frequently, not allowing time for a return to baseline, prolactin concentrations will be significantly elevated throughout 24 h.

The magnitude of the prolactin response appears to vary during the day with a more marked response to suckling in the afternoon than in the morning (Glasier et al, 1984). Elevated levels of prolactin during the night may be important in the maintenance of amenorrhoea associated with breastfeeding, as will be discussed later in this chapter. The amount of prolactin released in response to a single suckling episode does not appear to correlate directly with the volume of milk taken by the infant during that suckling episode, nor does it appear to have any bearing on the amount of milk available at the next feed.

The magnitude of the prolactin response may, however, be related to the strength or intensity of the suckling stimulus although intensity of suckling has so far been impossible to quantify in the human. However, it is quite clear that basal concentrations of prolactin are higher than normal in red deer who are underfed (Loudon et al, 1983) and perhaps in women who are malnourished (Lunn et al. 1981). In both instances the need for the offspring to suck harder to obtain adequate quantities of milk may result in an increased suckling intensity. Although we have been unable to demonstrate

a direct relationship between the amount of prolactin secreted in response to a discrete suckling episode and the amount of milk produced, a number of workers have shown that increasing prolactin concentrations in women by the administration of dopamine antagonists, such as sulpiride or metaclopramide, will result in a significant increase in milk yield (Ylikorkala et al, 1982).

Mechanisms underlying the release of prolactin during suckling are poorly understood and much of the work has been carried out in the rat which may differ considerably from the human in this area (see McNeilly, 1988). However, evidence from animal studies suggests that suckling at the nipple may result in changes in dopamine turnover, allowing prolactin to be released into the circulation. The changes in dopamine turnover may be secondary to suckling-induced increases in opioids such as β-endorphin (Gordon et al, 1987) which may also influence release of gonadotrophin-releasing hormone (GnRH). There has been a report of increases in plasma β-endorphin concentrations during suckling in women (Franceschini et al, 1989) but a direct relationship has yet to be confirmed.

While necessary for milk production in ruminants, growth hormone does not appear to be essential for lactogenesis in the human. Women with an isolated growth hormone deficiency can breastfeed successfully (Rimoin et al, 1968) and acute changes in growth hormone concentrations with suckling have not been identified. Similarly, changes in insulin and corticosteroid concentrations have been described in relation to suckling in some species but not in the human although lactation is associated with an alteration in general metabolism (Illingworth et al, 1986). Finally, both free and bound levels of thyroxine are reduced and thyroid hormone-binding globulin levels increased during lactation in women although there appears to be no specific role for these hormones in milk production.

During lactation, milk is continuously secreted into the alveoli. Oxytocin causes contraction of the myoepithelial cells, expelling milk from the alveoli and alveolar ducts towards the nipple. The mechanism underlying this—the milk ejection reflex—seems to be common to all mammals. Afferent impulses from the areola, stimulated by the baby suckling, promote release of oxytocin from the posterior pituitary (see Wakerley et al, 1988). In women, oxytocin is released even before the onset of suckling and the spontaneous ejection of milk often occurs in the absence of the suckling stimulus, particularly in response to associated stimuli such as the sound of the baby crying. It is now clear that oxytocin is secreted in pulses during the suckling episode (McNeilly et al, 1983) but the amount of oxytocin measured during suckling does not appear to be related to the amount of milk ejected. Secretion may be inhibited by both physical and psychological stress. In the light of this understanding, nasal administration of oxytocin, acting by facilitating the let down reflex, has been used with variable degrees of success in the treatment of women who are having difficulty establishing breastfeeding in the first few days postpartum. A rather more exciting prospect may be the possibility of enhancing the establishment of lactation, and therefore of successful breastfeeding, by administering an antiprogesterone such as RU-486 immediately after delivery to accelerate the initiation of milk secretion (Wolf et al, 1989).





### Milk composition

The composition of milk varies between species and within species. Composition also varies according to gestation, time postpartum and even within one suckling episode. In the human, milk composition during pregnancy is high in sodium and chloride and in lactoferrin and immunoglobulins but after parturition becomes rich in lactose with only moderate protein content. Precolostrum during pregnancy gives way to colostrum after delivery which persists for 4 or 5 days and is followed by so-called transitional milk for a further 5 days until mature milk is produced. Women who deliver prematurely produce milk of an immature composition.

Mature milk is made up of four major proteins (see Neville, 1983 for review). The two most important, nutritionally, are lactalbumin and lactoferrin. Although lactoferrin binds iron it is not important in providing the infant's iron requirements but does have bacteriostatic and bactericidal properties. Casein—the major protein present in cows' milk—is of less nutritional importance in human milk. The fourth major protein is immunoglobulin, mainly IgA, which accounts for about 10% of human milk protein. IgM and IgG are also present but in much smaller amounts.

Fat accounts for about 4% of human milk, mainly in the form of triglyceride contained in a milk fat globule. Fats are the major source of high-energy substrate, contributing about 40% of the calorie content. Fat is the most variable constituent changing even during a single suckling episode, being lower at the beginning than at the end of a feed. The fatty acid composition also varies with the maternal diet. Recent reduction in the intake of saturated fats in women in the USA has resulted in a significant change in the fatty acid composition of human milk (Guthrie et al, 1977).

The major sugar present in human milk is lactose. Serum albumin, lysozyme, some 30 enzymes, prolactin, minerals including a rich dietary source of calcium and phosphates are also found in significant quantities in human milk.

Recently a number of growth factors—polypeptides which stimulate proliferation and differentiation of a variety of cell types—have been characterized in human milk. The major one appears to be epidermal growth factor, but also present are insulin-like growth factor and transforming growth factors which have been implicated in the growth and progression of mammary tumours. Very little is known about their physiological role. Read et al (1986) have recently demonstrated that EGF from human milk will stimulate the proliferation of human fibroblasts in vitro and that included in the diet of weaning mice which have had 50% of the intestine resected, breast milk EGF will significantly accelerate intestinal growth. This in itself is not indicative of a physiological role in normal growth and development in vivo but it is interesting that the same workers have shown that EGF concentrations are significantly higher in milk from women who deliver prematurely.

### Infant nutrition

Most studies undertaken in developed countries have described daily milk

yields in the human of 700–900 ml. Based on these figures it is generally held, and indeed the World Health Organization in 1979 and again in 1985 advised, that while breast milk alone (i.e. unsupplemented) provides the optimal nutrition for the adequate growth of an infant for the first 4–6 months of life, supplements are required thereafter in most women. Others have suggested that unsupplemented breastfeeding may be inadequate beyond 3 months. At the other extreme Rattigan et al (1981) demonstrated that women living in Perth, Australia, had average daily milk yields of over one litre and that Perth babies could be exclusively breastfed for up to 15 months without showing faltering growth patterns. In practice, in most developed countries, supplementary food tends to be introduced at around 4–6 months of an infant's life. In the developing world the early introduction of supplements is, however, often associated with the introduction of gastrointestinal infection as a result of unhygienic preparation of artificial feeds and it can be argued that unsupported breastfeeding should be continued as long as the infant continues to grow normally (Kennedy et al, 1989).

Whether breastmilk is 'better' for babies in the absence of the unhygienic preparation of artificial feeds is still to be resolved. Most of the studies designed to answer this question have been too small or in some way methodologically flawed. Recently, Howie and colleagues in Dundee, Scotland, have undertaken an elegant and carefully controlled study following up a cohort of 750 women for 2 years (Howie et al, 1990). After correcting for all the variables associated with the choice of infant feeding method, this group found a significant reduction in the incidence of gastrointestinal infections during the first year of life if women breastfed for more than 13 weeks postpartum. That it did not appear to matter whether breastfeeding was exclusive or supplemented from birth, suggests that the decrease in infection was due to a positive effect of breast milk or breastfeeding *per se* rather than to a negative effect associated with artificial feeding. In support of these findings is a study undertaken recently in premature babies being cared for in a special care baby unit. Lucas et al (1988) showed that babies randomly allocated to receive expressed breast milk given by nasogastric tube were weaned off tube feeding significantly earlier than babies in the same unit receiving formula milk.

## Maternal nutrition

Both the quantity and quality of breast milk are affected by maternal nutrition. The World Health Organization (1985) undertook a collaborative study in Guatemala, Hungary, Sweden, Zaire and the Philippines, measuring amounts and composition of breast milk at regular intervals for 18 months postpartum. The quantity of breast milk was found to depend on many factors including the feeding routine adopted, the child's health and appetite and the availability of food other than breast milk. The quantity of milk in the first 3–4 months of lactation was significantly higher for Swedish mothers but, in the later months, differences between the groups were less clear. There were notable differences in breast milk composition between



countries. The total energy content, for example, was highest in Swedish mothers and there were substantial differences in nitrogen content between Guatemalan and Philippine mothers. In this study, in all the children assessed as above average for nutritional status, breast milk intakes were significantly greater than in children assessed as being of below average nutritional status; however, this should not be interpreted as meaning that the difference in nutritional status is due to the difference in breast milk intake as many of the children were also being given supplements. There were no correlations between characteristics of the mothers or the children and either the concentrations of the main breast milk constituents or its energy content.

## Effects of lactation on fertility

The mechanism by which breastfeeding affects ovarian activity is not clear. In women who choose not to breastfeed, menses usually returns at around 9 weeks postpartum (Howie et al, 1982). The first bleeding is not usually preceded by ovulation which in our studies recurred at a mean of 13 weeks following delivery (range 11–21). Among bottlefeeding women, FSH concentrations return to normal follicular phase levels within 4 weeks postpartum (Glasier et al, 1983). The normal pulsatile pattern of LH secretion, however, takes longer to return and it is probably the timing of its return which determines the resumption of ovulatory ovarian cycles (Glasier et al, 1984). Perhaps because of abnormal pulsatile LH secretion, early cycles in these women are often anovulatory or have an inadequate luteal phase. Serum prolactin concentrations return to normal, non-pregnant levels within 4 weeks postpartum if breastfeeding does not occur (McNeilly et al, 1982). The delay in the resumption of normal ovulatory cycles in the absence of lactation depends mainly, if not exclusively, on the time taken by the hypothalamo–pituitary–ovarian axis to recover from the suppressive effects of pregnancy.

In our own studies undertaken in Edinburgh, the mean time for the resumption of menstruation among women who breastfed their infants was 28 weeks (range 15–48) after delivery, while the mean time for first ovulation was 34 (range 14–51) weeks. As with bottlefeeding women, first cycles and indeed many subsequent cycles occurring while breastfeeding continues are anovulatory or have aberrant luteal phases (McNeilly et al, 1982). The timing of the resumption of fertility in women who do breastfeed appears to depend mainly on the pattern of infant feeding. Howie et al (1981) found that full breastfeeding was associated with the suppression of ovarian activity but that once food other than breast milk was given to the baby in any quantity, ovarian activity returned (Figure 4). The duration of lactational amenorrhoea was highly correlated with the frequency and duration of suckling, i.e. the amount of time the baby spent at the breast. Like bottlefeeders, even if breastfeeding does occur, serum FSH concentrations return to normal by 4 weeks postpartum and there is no evidence to suggest that ovarian suppression is the result of any abnormality of FSH secretion. It is quite clear, however, that there is a disturbance of pulsatile

LH secretion during lactation (Figure 5). In the early postpartum weeks during full breastfeeding there is complete suppression of pulsatile LH secretion. Throughout the period of amenorrhoea, even if it persists later into the puerperium (up to 24 weeks), suppression of LH pulsatility may be seen (Glasier et al, 1984). As suckling activity decreases there is a gradual return of pulsatility, probably occurring first at night as it does with the onset

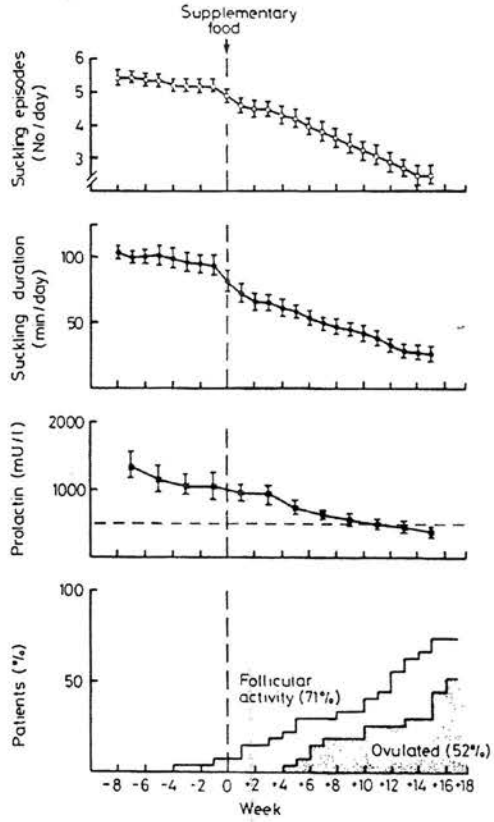


**Figure 4.** Mean 24 h suckling frequency and duration and mean prolactin concentration in samples taken every 2 weeks from 27 breastfeeding women shown in relation to the time of first introducing supplementary food. The percentage of women who showed evidence of follicular development and of ovulation are shown in the bottom figure. From Howie et al (1981) with permission.



of puberty. Abnormal pulse patterns persist during (and may indeed be responsible for) the aberrant cycles seen at the end of lactation.

What causes the disturbance of LH secretion remains to be determined. Stimulation of the nipple acting via changes in opioid secretion may inhibit the pulse generator, in its turn inhibiting a normal pattern of GnRH release. Ovulation can be induced as early as 6 weeks postpartum in women by the pulsatile infusion of exogenous GnRH (Glasier et al, 1986).

As pathological hyperprolactinaemia is associated with disturbances of pulsatile LH secretion and amenorrhoea in women, it has often been assumed that the hyperprolactinaemia induced by suckling is responsible for suppressing ovarian activity. Prolactin concentrations are certainly raised during breastfeeding and (as discussed) suckling episodes are associated with an acute release of prolactin. As suckling activity declines so do serum prolactin concentrations such that by the time ovarian activity resumes

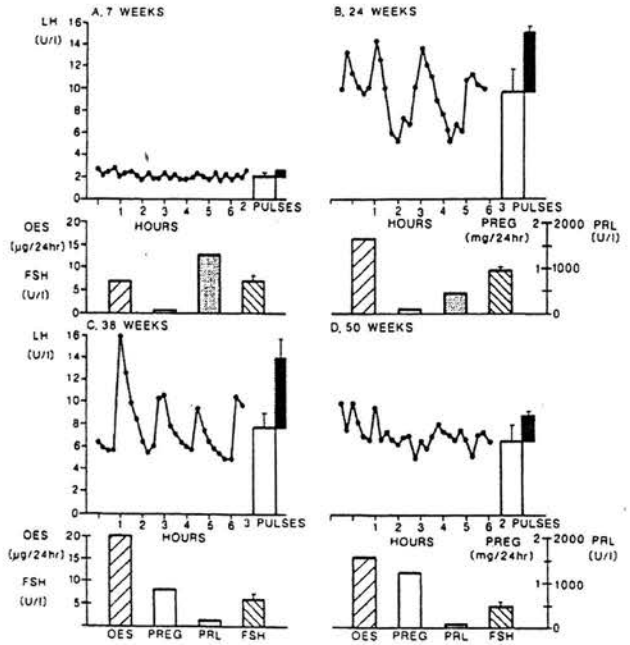


**Figure 5.** The pattern of LH secretion in one breastfeeding woman during the postpartum period. The mean frequency □ and amplitude ■ of LH pulses is shown in the top figure while mean concentrations of serum FSH and prolactin and urinary oestrogen and pregnanediol at the time of sampling are shown in the lower figures. From Glasier et al (1984a).

prolactin levels are approaching normal. Moreover, inhibitors of prolactin secretion such as bromocriptine, given to women postpartum, result in a rapid decrease in serum prolactin followed by a rise in oestrogen. However, the administration of bromocriptine also results in the cessation of milk secretion so that the effects of suckling are inhibited. Thus, it may be that hyperprolactinaemia is simply a marker of suckling activity and of milk production rather than a mechanism by which ovarian activity is suppressed (McNeilly, 1987).

Gordon and Williams (1989) have recently demonstrated that if infant monkeys are allowed only restricted access to the nipple (limiting suckling to either day time or night time) despite prolactin concentrations being within the non-lactating range for half of the day, the duration of suppression of ovulation is no different from monkeys allowed unrestricted suckling. It is interesting to note that the diurnal rhythm of prolactin secretion seen in non-breastfeeding women appears to be maintained during lactation (Tay et al. 1989). Thus, when the pulsatile secretion of LH resumes first during the night, it is at a time when prolactin concentrations are at their highest making it illogical to argue that there is a direct effect of prolactin on GnRH release.

Based on the data available to date, the most plausible explanation of the effect of lactation on fertility is as follows (McNeilly et al, 1985). Immediately after delivery, as a result of high concentrations of ovarian steroids during pregnancy, pulsatile LH secretion is suppressed. With time and in the absence of breastfeeding, LH secretion returns to normal and in the presence of an early resumption of normal FSH secretion, ovarian activity returns. If breastfeeding occurs, the effect of the baby suckling at the nipple (acting perhaps via opioidergic mechanisms) inhibits the normal pattern of GnRH release, resulting in a disturbance of pulsatile LH and suppression of ovarian activity. With the passage of time and the recovery from pregnancy, LH secretion resumes, at least for some part of the day. However, the hypothalamo–pituitary system in women postpartum is known to have an increased sensitivity to the negative feedback effects of oestrogen (Baird et al, 1979). Thus, when pulsatile LH secretion is sufficient to initiate follicle growth, as soon as the granulosa cells start to secrete measurable amounts of oestrogen, this acts in the negative feedback loop to switch off LH secretion and the follicle becomes atretic without stimulating endometrial growth. Once suckling activity declines and nipple stimulation becomes increasingly infrequent, LH pulsatility is maintained in a normal pattern for longer periods of time. The sensitivity of the hypothalamus to the negative feedback effects of oestrogen gradually returns to normal, follicle growth and oestrogen production can be sustained long enough to stimulate endometrial proliferation and vaginal bleeding can then occur. Individual women probably differ in their sensitivity to the suckling stimulus and so the duration of lactational amenorrhoea varies among individuals as well as according to the amount of time the baby spends at the breast.

### Maternal nutritional status and the resumption of fertility

Differences clearly do exist between populations in the duration of lactational amenorrhoea which may be partly a result of differences in maternal nutrition (Ramchandran, 1985). Weight loss in women of reproductive years is known to cause amenorrhoea and periods of acute famine are associated with changes in fertility rates (Bongaarts, 1980).



A number of studies have investigated the relationship between the duration of lactational amenorrhoea postpartum or the interbirth interval and maternal nutrition. The two major problems confronting every study are how to measure nutritional status and how to correct for breastfeeding activity as a confounding variable. Large demographic studies using socio-economic status (Salber et al, 1966) or maternal dietary intake (Careal, 1978) to measure nutritional status have demonstrated a reduction in the duration of amenorrhoea in more prosperous societies. However, these differences may well reflect a difference in infant feeding patterns on which little or no information is available. Smaller studies using physiological parameters such as weight, ponderal index or serum albumin levels as an index of maternal nutrition have suggested that large differences in maternal weight may be associated with an alteration in the duration of lactational amenorrhoea; but once again there is no evidence that the effect is independent of breastfeeding practices.

Carefully controlled studies of maternal dietary supplementation show most promise. In a study undertaken in Gambia, Lunn et al (1981) provided a supplement of approximately 720 kcals/day during pregnancy and lactation. Fertility—as measured by plasma concentrations of oestrogen, progesterone and prolactin—was shown to return 21 weeks earlier in women who received supplements compared with those who did not. As the mothers were observed to be eating the supplements provided, the effect may well have been due to the alteration in maternal nutritional status. However, changes in suckling patterns were not well documented and plasma samples were taken very infrequently; moreover much emphasis was placed on prolactin concentration as an index of normal fertility.

In conclusion, the available evidence suggests that nutritional status does have some effect on the duration of lactational infertility but the effect is very small unless malnutrition is moderate or severe. Moreover, the effect may well be mediated by an alteration in suckling activity rather than by a direct effect of nutritional intake on the hypothalamo–pituitary–ovarian axis.

### Contraception during lactation

While breastfeeding is the only method of birth spacing used in some cultures, most women prefer to use an artificial means to postpone subsequent pregnancies. In developed countries the combined oral contraceptive pill is the most widely used contraceptive preparation but, while not strictly contra-indicated during lactation, most clinicians advise against its use. Oestrogen does enter the breast milk although not in amounts which are sufficient to have an adverse effect on the baby. Indeed most formula milk preparations are derived from cows' milk which has very high concentrations of oestrogen. It is clear, however, that the use of oestrogen-containing contraceptives does

have a significant negative effect on milk yield (Koetsawang, 1982). Gestagen-only preparations do not influence milk output and are widely prescribed either as oral or as parenteral depot preparations during breastfeeding. Mechanical methods of contraception present no particular problems during breastfeeding.

The use of a long-acting agonist analogue of GnRH as a contraceptive for breastfeeding mothers has recently been investigated. The theoretical advantage of this preparation lies in the fact that only a small amount passes into the breast milk and, presumably because of inactivation in the stomach, is without biological activity in the infant (Dewart et al, 1987). Fraser et al (1989) have shown the analogue, given as a nasal spray, to be effective in suppressing ovarian activity during the postpartum period. The effects of the GnRH analogue in a slow-release depot form, which would be a much more practical means of administration are now being investigated.

Perhaps more critical than the means of contraception chosen is the time postpartum when it should be introduced. It is quite clear that breastfeeding alone affords some protection against pregnancy and yet it is the norm in most countries to advise the early use of an artificial method of contraception, i.e. if not immediately postpartum, then by 6 weeks after delivery. There is abundant evidence to suggest that, in developing countries, most people only use prescribed contraceptives for a maximum of 6 months (Laukaran, 1981). If the introduction of a contraceptive preparation is delayed until it is really necessary, interbirth intervals may be significantly prolonged thus improving the health of both mother and infant and influencing population growth. To this end a group of international agencies responsible for health care met in 1988 and produced a consensus statement suggesting that the introduction of artificial methods of contraception could be delayed until 6 months postpartum as long as women remained amenorrhoeic and were fully or almost fully breastfeeding their infants (Kennedy et al, 1989).

## BREASTFEEDING AND BREAST CANCER

A number of studies have been undertaken to investigate the relationship between breastfeeding and the incidence of breast cancer. Breast cancer is a disease of developed countries in which the incidence of breastfeeding, particularly for long periods of time, is low. In a large multinational study carried out by MacMahon et al (1970) it was clear that high parity was associated with a decreased risk of developing breast cancer but that lactation itself contributed no extra protection. Even women who lactated for 5 years or more occurred no less frequently among cancer cases than among controls. These findings were recently confirmed in a Scandinavian study of over 50 000 parous women (Kvale and Heuch, 1987). Other studies have, however, demonstrated a protective effect. In Shanghai, where admittedly the incidence of breast cancer is extremely low, delayed age of first full-term delivery or nulliparity were both associated with an increased risk of developing the disease while increasing parity reduced the risk—women with five or more children had only 39% of the risk held by women with only one child (Yuan et al, 1988). Breastfeeding for a total of more than 9 years reduced the risk by 63% when compared with women who breastfed for a total of only 3 years or less. Two case control studies from North America (Byers et al, 1985; McTiernan and Thomas, 1986) and one from South Africa have confirmed these findings. The incidence of breast cancer in both pre- and postmenopausal women was reduced among breastfeeders but only among women with premenopausal cancer was there a direct relationship between the duration of lactation and the reduction in the risk.

The mechanisms by which lactation could protect against breast cancer are not clear. The hormonal changes associated with breastfeeding may, in some way, inhibit tumour initiation; alternatively the inhibition of ovulation and of cyclical changes in the breast may have a protective effect. More work needs to be done in the area before any greater understanding can be reached.



## SUMMARY

The development of the human breast is dependent on the presence of ovarian steroids. The basic secretory units—the alveoli—continue to respond to steroids throughout the reproductive years. Lactogenesis is triggered by a rapid and drastic fall in progesterone at delivery and maintained by prolactin while the actual expulsion of milk from the breast depends on oxytocin. The composition of milk is very variable but is adequate to provide the sole source of nutrients for up to the first 6 months of life. Lactation suppresses ovarian activity probably through a disturbance in the pulsatile pattern of LH secretion but the degree of suppression depends on infant feeding patterns and perhaps on maternal nutritional status. Breastfeeding therefore confers a degree of protection against pregnancy but some artificial methods of contraception are appropriate for use during lactation. It is still not clear whether breastfeeding protects significantly against breast cancer.

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# Twenty-four hour patterns of prolactin secretion during lactation and the relationship to suckling and the resumption of fertility in breast-feeding women

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**In breast-feeding women prolactin released in response to suckling is essential for the maintenance of lactation. This physiological hyperprolactinaemia is also associated with lactational infertility. However, it is not clear whether there is any direct relationship between changes in prolactin *per se* and the duration of infertility. To address this question, our study determined the pattern of prolactin secretion in relation to suckling and the return of ovarian activity in the same cohort of breast-feeding women. Blood samples were withdrawn at 10 min intervals for 24 h from 09:00 to 09:00 h at either 4 ($n$ = 9) or 8 weeks ($n$ = 11) post-partum when the women had completely suppressed ovarian activity, at the time of the introduction of supplements to the baby ($n$ = 17), a time associated with reduction of suckling activity, at first menses while still breast-feeding ($n$ = 13) and in the follicular phase ($n$ = 9) of the first menstrual cycle after weaning. During sampling, mothers and babies continued their normal pattern of suckling activity. The pattern of prolactin release was very variable at each stage of lactation, depending on the pattern of suckling. Frequent suckling was associated with elevated prolactin concentrations during the 24 h period throughout lactation. When suckling was less frequent, prolactin concentrations fell to baseline values between breast-feeds, but prolactin was released in response to all suckling episodes. An increase in prolactin concentrations at night, independent of suckling, was only evident once breast-feeding had ceased. The prolactin response to suckling declined significantly only after the return of menses at 33.6 ± 3.5 weeks post-partum. There was no relationship between the duration of amenorrhoea and the plasma concentrations of prolactin over 24 h, or day or night separately, throughout lactation. However, there was a strong correlation ($r$ = 0.843; $P < 0.01$) between the timing of the introduction of dietary supplements to the baby and the duration of amenorrhoea. These results suggest that there may be no precise link between the release of prolactin during lactation and the duration of lactational infertility in breast-feeding women.**

*Key words:* infertility/lactation/prolactin release/suckling

## Introduction

Prolactin is essential for the initiation of lactation (McNeilly, 1977; Glasier and McNeilly, 1990). The administration of dopamine agonists, such as bromocriptine which decrease prolactin secretion, results in the inhibition of milk production (Cooké *et al.*, 1976; Martin *et al.*, 1981). However, in women the relationship between prolactin secretion and the maintenance of lactation is not clear. In breast-feeding women, basal prolactin concentrations fall as suckling activity declines with time post-partum (Howie *et al.*, 1981; Andersen and Schioler, 1982), although individual suckling episodes are associated with an acute rise in prolactin concentrations even after prolonged lactation (Madden *et al.*, 1978; Gross *et al.*, 1979; McNeilly *et al.*, 1983). While daily milk output and the yield during an individual suckling episode were correlated with basal prolactin concentrations in one study (Hennart *et al.*, 1981), there was no relationship found between the acute rise in prolactin concentrations and the amount of milk produced during a single suckling episode (Howie *et al.*, 1979; Glasier *et al.*, 1984; Unvas-Moberg *et al.*, 1990). Nevertheless, the administration of dopamine agonists, such as metoclopramide (Kauppila *et al.*, 1981) or sulpiride (Aono *et al.*, 1982; Ylikorkala *et al.*, 1982) which increase prolactin concentrations, have been shown to improve milk output in women.

Whether or not prolactin has an instrumental role in the mechanisms underlying lactational amenorrhoea has not been resolved (McNeilly, 1994). However, one investigator (Diaz *et al.*, 1988, 1991) has suggested that women who show a more marked prolactin rise in response to individual suckling episodes experience a longer duration of amenorrhoea. To test this hypothesis further, we investigated the pattern of prolactin secretion in breast-feeding women for 24 h at different times during the post-partum period and related the changes in prolactin response to the duration of lactational infertility.

## Materials and methods

### *Subjects and sampling methods*

A total of 20 women who intended to breast-feed their infants were recruited from the postnatal wards of the Simpson Memorial Maternity Pavilion (SMMP), Royal Infirmary, Edinburgh, UK. They were aged between 18 and 35 years, and in good general health with no history of infertility. They had delivered a healthy infant weighing >2.5 kg. None were using steroidal contraception while breast-feeding. The infant feeding pattern was recorded daily. Night-time suckling episodes

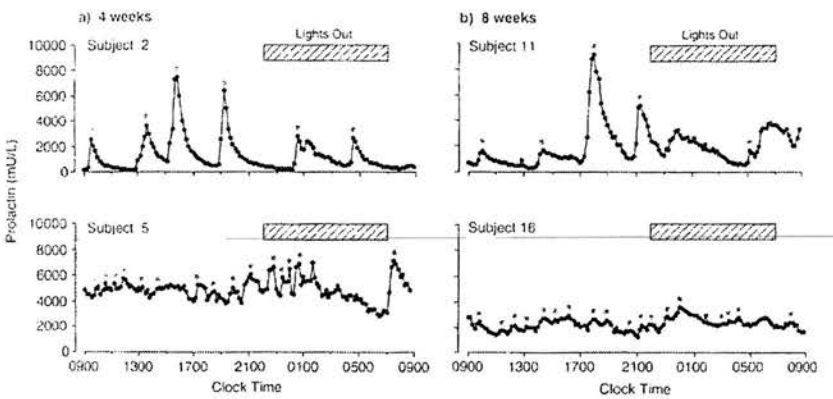


**Figure 1.** Changes in the plasma concentrations of prolactin over a 24 h period for four individual women at **(a)** 4 or **(b)** 8 weeks post-partum. The asterisks indicate a suckling episode.

**Table I.** Comparison of the concentrations (mean ± SE) of prolactin over each 24 h sampling period and during daytime (07:00–22:00 h) and night-time (22:00–07:00 h) at different stages of lactation in breast-feeding women

| Stage of lactation | No. of subjects | Mean plasma prolactin concentration (mIU/l) | | |
|---|---|---|---|---|
| | | Overall 24 h | Day | Night |
| 4 weeks | 9 | 2434 ± 409 | 2325 ± 436 | 2543 ± 433 |
| 8 weeks | 11 | 2253 ± 443 | 2138 ± 525 | 2530 ± 397 |
| Introduction of dietary supplements to the baby | 14 | 1404 ± 223 | 1301 ± 222 | 1580 ± 260 |
| First menses | 13 | 463 ± 102 | 386 ± 95 | 618 ± 121[a] |
| After weaning | 9 | 166 ± 14 | 113 ± 14 | 256 ± 20[b] |

[a] $P < 0.05$ compared with daytime.
[b] $P < 0.001$ compared with daytime.

were defined as those which occurred between 22:00 and 07:00 h. Any supplementary food given to the baby other than breast milk was recorded.

At four key stages of the study, the women were admitted with their infants to the Clinical Research Unit of the SMMP for serial blood sampling throughout 24 h. The first admission was at either 4 ($n$ = 9) or 8 weeks ($n$ = 11) post-partum when the mothers were fully breast-feeding and ovarian activity was fully suppressed. The second serial blood sampling was within 1 week of the introduction of supplementary food to the baby ($n$ = 14), mothers having been encouraged to supplement their babies' diets by health visitors and/or friends and relatives. The third study period was within a few days following the onset of the first menstrual period while the mothers were still partially breast-feeding ($n$ = 13). Finally, the women were studied in the early follicular phase of a normal menstrual cycle after the complete cessation of breast-feeding ($n$ = 9).

During blood sampling, no restrictions were made on physical activity or food intake beyond that placed by a hospital environment, and the women slept at night according to their usual pattern. Breast-feeding took place on demand, and the time of onset of suckling and the duration of each feed were noted in detail. In addition, the activities of the women, including meal times and sleep patterns, were recorded. On admission to the unit at 08:30 h a 20 gauge Venflon cannula was inserted into a forearm vein and the cannula kept patent with heparinized saline. From 09:00 h, 2.5 ml venous blood samples were collected every 10 min throughout 24 h. At night during sleep, blood samples were collected through a long i.v. catheter which passed through a hole in the wall to the adjoining laboratory, allowing blood samples to be collected without disturbing the women's sleep. Lights were switched off between 23:00 and 07:00 h. The plasma was separated and stored at –20°C until assayed for prolactin in batches.

The study was approved by the Lothian Health Board Ethics of Medical Research Committee and informed consent was obtained from all the women.

### *Hormone assays*

Plasma prolactin concentrations were measured in a two-site immunoradiometric assay (Netria, St Bartholomew's Hospital, London, UK; Wu *et al.*, 1990). The intra- and interassay coefficients of variation were <8 and <11% respectively.

### *Statistical analysis*

The data are presented as mean ± SEM except where otherwise stated. Comparisons between mean hormonal concentrations were performed by an analysis of variance on log-transformed data. The prolactin response to suckling was determined by the difference between the increments in plasma concentrations of prolactin at 10, 20 and 30 min following the onset of suckling and a comparison between the maximum prolactin concentration in response to suckling.

## Results

Mean plasma concentrations of prolactin in relation to time post-partum are shown in Table I. During full breast-feeding in

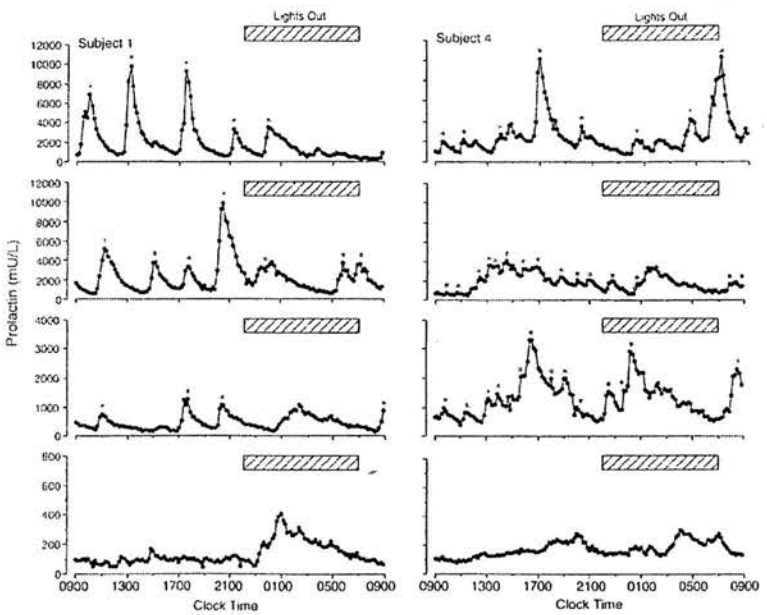


**Figure 2.** Changes in the plasma concentrations of prolactin over a 24 h period in two individual women measured at **(a)** 4 weeks post-partum, **(b)** within 1 week of the introduction of dietary supplements to the baby, **(c)** in the follicular phase of the cycle following first menses and **(d)** in the follicular phase of the cycle after weaning. The asterisks indicate a suckling episode.

the early post-partum weeks, the mean prolactin concentrations were significantly ($P < 0.001$) higher than after weaning and when compared with concentrations measured at the time of the introduction of dietary supplements to the baby ($P < 0.05$). However there were no differences between women sampled at 4 weeks compared with 8 weeks post-partum. Dietary supplements were introduced at a mean of 14.9 ± 0.9 weeks post-partum (range 9–24 weeks) for reasons unrelated to milk production. At this time mean concentrations of prolactin were still significantly ($P < 0.001$) higher than after the babies had been weaned. The introduction of supplements coincided with a sustained decline in suckling duration 3.6 ± 1.0 weeks later (range 0–22) and suckling frequency at 6.9 ± 1.7 weeks (range 1–22). The decline in suckling duration preceded the decline in frequency in every individual. The return of menses occurred at a mean of 33.6 ± 3.5 weeks post-partum (range 16–65), and mean prolactin concentrations remained significantly elevated (over baseline; $P < 0.05$) at this time. Only after the resumption of menses was there a significant ($P < 0.005$) rise in prolactin concentration at night-time (compared with daytime), when 10 of the 13 women studied at this time breast-fed their babies between 22:00 and 07:00 h. The night-time rise in prolactin concentration was more marked ($P < 0.001$) once breast-feeding had ceased.

Representative patterns of prolactin secretion among individual fully breast-feeding women are shown in Figure 1. When suckling episodes occurred very frequently (subject 5 at 4 weeks; subject 16 at 8 weeks), prolactin concentrations remained above baseline throughout the 24 h period and a discrete response to every suckling episode was difficult to define. This was in contrast to less frequent suckling (subject 2 at 4 weeks; subject 11 at 8 weeks) when the prolactin concentrations fell to baseline values between breast-feeds, while each feed was accompanied by a marked and clearly defined rise in prolactin concentration.

Frequent suckling was associated with a sustained rise in basal prolactin concentrations throughout lactation, even at the time of resumption of menses. Figure 2 shows the 24 h pattern of prolactin secretion at four time-periods for two subjects. Subject 4 maintained a high suckling frequency and was still breast-feeding her baby 13 times during the 24 h when she was sampled following first menses. In contrast, subject 1 breast-fed much less frequently and reduced to four feeds per day by the time menses resumed. In each subject a decline in 24 h prolactin concentrations occurred with time post-partum. Suckling was always accompanied by a rise in prolactin concentration, but the magnitude of this rise also decreased with time.

The mean prolactin response over the first 30 min after the start of suckling at each post-partum period is shown in Figure 3. There was no significant difference in the prolactin response in terms of either the amount of hormone released or the maximum prolactin concentration achieved during suckling episodes at 4 and 8 weeks post-partum. At the time of introducing dietary supplements to the baby, prolactin responses to suckling were reduced, although this was not significant, but the response was significantly ($P < 0.05$) reduced after the return of menses.

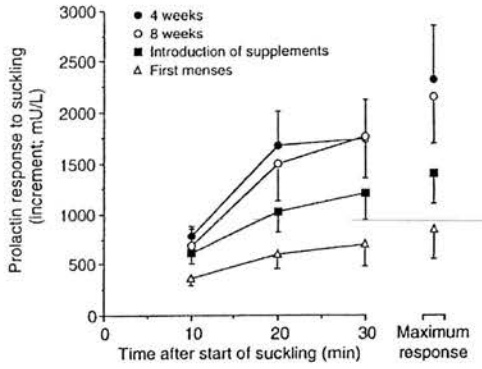


**Figure 3.** Changes in the incremental prolactin response and the maximum incremental response to suckling at various times post-partum.

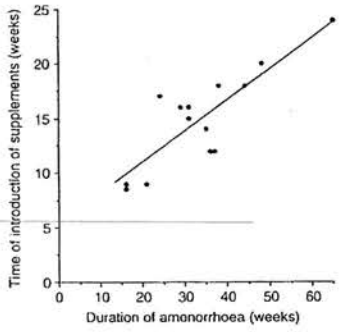


**Figure 4.** The relationship between the duration of amenorrhoea and the time when supplementary feeds were introduced to the baby.

**Table II.** Relationship in individual subjects ($n = 14$) between the duration of amenorrhoea, time of introduction of supplements to the baby and suckling frequency and the mean (±SEM) plasma concentrations of prolactin over 24 h, during daytime (07:00–22:00 h) and night-time (22:00–07:00 h), and the mean increment in prolactin in response to suckling throughout the 24 h period of sampling at the time of the introduction of supplements

| Subject no. | Duration of amenorrhoea (weeks) | Time of introduction of supplements (weeks) | Suckling frequency (day/night) | Plasma concentrations of prolactin (mIU/l) | | | |
|---|---|---|---|---|---|---|---|
| | | | | Over 24 h | Daytime | Night-time | Mean prolactin increment in response to suckling |
| 15 | 65 | 24 | 7/0 | 905 ± 28 | 907 ± 41 | 901 ± 43 | 331 ± 74 |
| 11 | 48 | 20 | 7/0 | 1064 ± 45 | 854 ± 54 | 1525 ± 45 | 675 ± 254 |
| 10 | 44 | 18 | 5/1 | 1093 ± 51 | 732 ± 42 | 1616 ± 72 | 715 ± 135 |
| 6 | 38 | 18 | 8/1 | 1227 ± 49 | 1279 ± 78 | 1073 ± 31 | 688 ± 144 |
| 3 | 37 | 12 | 6/3 | 919 ± 52 | 715 ± 44 | 1324 ± 112 | 1103 ± 275 |
| 2 | 36 | 12 | 5/2 | 660 ± 45 | 728 ± 70 | 627 ± 49 | 1564 ± 411 |
| 14 | 35 | 14 | 9/2 | 1855 ± 95 | 2260 ± 142 | 1358 ± 90 | 1482 ± 366 |
| 5 | 31 | 15 | 6/0 | 1505 ± 50 | 1430 ± 66 | 1783 ± 75 | 962 ± 306 |
| 16 | 31 | 16 | 5/2 | 1155 ± 88 | 532 ± 21 | 2247 ± 163 | 760 ± 282 |
| 13 | 29 | 16 | 3/0 | 397 ± 21 | 257 ± 24 | 605 ± 20 | 606 ± 77 |
| 4[a] | 24[a] | 17 | 11/2 | 1867 ± 77 | 2027 ± 113 | 1744 ± 105 | 892 ± 204 |
| 12 | 21 | 9 | 9/1 | 4386 ± 188 | 390 ± 242 | 5233 ± 324 | 4556 ± 571 |
| 18 | 16 | 9 | 5/1 | 962 ± 72 | 927 ± 105 | 825 ± 40 | 2500 ± 628 |
| 1 | 16 | 9 | 5/2 | 2278 ± 224 | 2486 ± 224 | 1941 ± 136 | 4336 ± 1086 |

[a]Weaned abruptly.

The relationships between the timing of the introduction of supplements, suckling frequency, the duration of amenorrhoea and patterns of prolactin secretion are shown in Table II for the 14 women who were sampled within 1 week of starting to give their baby dietary supplements. The timing of the introduction of supplements and suckling frequency varied considerably. The duration of amenorrhoea was strongly correlated ($r = 0.843$; $P < 0.01$) with the timing of the introduction of supplements (Figure 4). No clear relationship for the duration of lactational amenorrhoea could be found with suckling frequency at the time when supplements were started, mean plasma concentrations of prolactin, either for the 24 h period or for day and night separately, or the mean prolactin increment in response to suckling.

## Discussion

While it is accepted that prolactin concentrations in breast-feeding women fall with time post-partum despite sustained lactation (e.g. Howie *et al.*, 1981; Andersen and Schioler, 1982; Howie and McNeilly, 1982), our study has demonstrated that the immediate response of prolactin to suckling also decreased with time, regardless of the suckling frequency or time of suckling during a 24 h period. These results extend those of Nunley *et al.* (1991), who investigated the pulsatile release of prolactin during lactation. They concluded that both the amount of prolactin secreted and the rate of release of prolactin at each release episode decreased with time, while the frequency of release episodes remained the same. However, the suckling pattern of the individuals studied was not recorded, and so it is not possible to distinguish between spontaneous prolactin release and suckling-induced release in their study. Here, we have been unable to identify the clear spontaneous pulsatile secretion of prolactin unrelated to suckling.

We were unable to identify a nocturnal rise in prolactin concentration in the early post-partum weeks. A nocturnal rise in prolactin concentration in non-lactating women has been recognized for many years (Sassin *et al.*, 1973) and can be

demonstrated in women who do not breast-feed their babies as early as 10 days after childbirth (Liu and Park, 1988). Previous studies have suggested that suckling episodes which occur in the morning are associated with a less marked prolactin response than those occurring in the afternoon, particularly after 13 weeks post-partum (Glasier *et al.*, 1984; Diaz *et al.*, 1988). These results were interpreted as indicating an altered sensitivity of the hypothalamus to the effects of suckling on the release of prolactin (Glasier *et al.*, 1984). Certainly there does not appear to be any lack of releasable prolactin in the pituitary at least after 12 weeks post-partum (Tay *et al.*, 1993). In our study there were indications in some women of an increased release of prolactin in response to suckling during the afternoon and evening (Figure 1, subjects 2 and 11; Figure 2, subject 4) but this was not a significant finding. However, an analysis of the changes in mean prolactin concentrations over the 24 h periods of observation indicated a significantly higher level at night-time (between 22:00 and 07:00 h) than during the daytime (between 07:00 and 22:00 h), but only after first menses while breast-feeding, and then after weaning (Table I). It is possible that the nocturnal rise in prolactin concentration is less noticeable during the early post-partum weeks when daytime suckling frequencies are high, inter-suckling intervals short and basal prolactin concentrations elevated. It was noticeable that when suckling frequencies were high, lack of suckling during the night was associated with a decline in plasma prolactin concentration, until suckling occurred, when values increased (Figure 1, subject 11 and Figure 2).

In our study the periods of sampling were chosen to coincide with episodes which we have shown to be associated with aspects of the return of fertility in breast-feeding mothers. Thus, the introduction of dietary supplements to the baby in the particular study cohort in Edinburgh, UK is associated with a reduction in suckling frequency; the resumption of ovarian activity (Howie *et al.*, 1981) and the menstrual cycle after first menses while breast-feeding continues is associated with inadequate luteal phases (McNeilly *et al.*, 1982). It was hoped that sampling at these times might identify any alteration in the prolactin responses to suckling which might be related to the duration of amenorrhoea in the former case or luteal function in the latter.

In previous studies in Chile, it has been shown that an increased prolactin response to suckling was associated with a longer duration of amenorrhoea (Diaz *et al.*, 1988, 1991). In contrast, we were unable to identify any relationship between the magnitude of the prolactin response to suckling episodes and the duration of amenorrhoea. In our study, no restriction was placed on the way the mothers breast-fed their babies, and during the periods of sampling the mothers continued to suckle their babies normally. In contrast, in the Diaz *et al.* studies, all subjects were exclusively breast-feeding and amenorrhoeic when they were admitted to the study at 3–4 months post-partum, and the women were specifically asked to breast-feed exclusively (even water was not permitted) and to delay introducing dietary supplements to their babies for 6 months (Diaz *et al.*, 1988, 1991). It may be that this artificial restriction on the natural pattern of suckling resulted in the higher release of prolactin observed in the women with prolonged amenorrhoea (Diaz *et al.*, 1988, 1991). In our study we did not interfere with the natural pattern of suckling established by individual mothers and babies. Perhaps babies which were naturally frequent feeders would elicit a greater suckling stimulus and hence a greater release of prolactin if their suckling times were strictly regimented, as in the Chilean study.

While it is possible that any relationship between the prolactin response to suckling and the duration of amenorrhoea was missed in our study, the fact that we sampled women during normal breast-feeding suggests that the relationship between prolactin response and the duration of amenorrhoea is not strong. In contrast, in our study there was a strong correlation between the time of the introduction of dietary supplements to the baby and the duration of amenorrhoea (Figure 4). This confirms previous results in our study population (Howie *et al.*, 1981; Howie and McNeilly, 1982) and of others (Gray *et al.*, 1990). However, the effect of dietary supplements on the resumption of fertility varies within different societies and the type of supplement given (Lewis *et al.*, 1991; Kennedy and Visness, 1992).

The results of our study do not identify a specific pattern of prolactin release or an amount of prolactin released that is predictive of the duration of infertility in breast-feeding women. The pattern of suckling had a major impact on the changes in the plasma concentration of prolactin at all stages of lactation investigated. Thus, at present it is not possible to confirm that the increase in prolactin associated with breast-feeding is causally related to the suppression of fertility post-partum.

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# Abnormal twenty-four hour pattern of pulsatile luteinizing hormone secretion and the response to naloxone in women with hyperprolactinaemic amenorrhoea

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## Summary

**OBJECTIVE Hyperprolactinaemic amenorrhoea is associated with disturbances of pulsatile gonadotrophin secretion. The underlying mechanism remains unclear and the aim of this study was to investigate the 24-hour secretory pattern of gonadotrophins in women with hyperprolactinaemic amenorrhoea. The effect of opioid blockade using naloxone infusion on LH secretory pattern was also studied.**

**DESIGN The secretory patterns of LH, FSH, PRL and their responses to naloxone infusion were studied by serial blood samples collected at 10-minute intervals for 24 hours. On the following day, naloxone was infused at a dose of 1·6 mg per hour for 4 hours.**

**PATIENTS Eight women with hyperprolactinaemic amenorrhoea, two women hyperprolactinaemic but with normal ovarian cycles, and nine control subjects in the early follicular phase of menstrual cycle.**

**MEASUREMENTS Concentrations of LH, FSH and PRL were measured in plasma samples obtained at 10-minute intervals for 24 hours. In one woman, concentrations of urinary oestrone glucuronide were measured daily during treatment with pulsatile GnRH.**

**RESULTS The number of LH pulses per 24 hours was significantly fewer in women with hyperprolactinaemic amenorrhoea than in those with hyperprolactinaemia with normal cycles or control subjects (mean ± SEM 4·5 ± 2·4 *vs* 13·5 ± 2·5 *vs* 17·3 ± 0·8, $P < 0·001$). The magnitude of each episode of secretion was significantly higher in the hyperprolactinaemic amenorrhoeic women ($P < 0·05$) so the overall mean concentrations of LH throughout the 24-hour period was similar in the three groups (5·2 ± 1·1, 4·8 ± 0·8 and 5·2 ± 0·4 U/l respectively). In women with hyperprolactinaemic amenorrhoea there was no significant change in the pattern of LH secretion during sleep in contrast to the control women in whom there was a slowing in the LH pulse frequency during the night. There was no significant change in the mean concentrations of LH, FSH and PRL during the naloxone infusion. There were also no significant changes in the LH pulse frequency in response to naloxone infusion when compared with an equivalent period of time in the previous 24 hours. In one hyperprolactinaemic amenorrhoeic woman, follicular development, ovulation and pregnancy were induced when gonadotrophin releasing hormone (GnRH) was infused in a pulsatile manner at a dose of 5 μg every 90 minutes.**

**CONCLUSIONS The suppression of normal ovarian cycles in women with hyperprolactinaemic amenorrhoea is due to a significant reduction in frequency of LH (GnRH) secretion which is not due to an increase in hypothalamic opioid activity. As normal ovarian cycles can occur or be induced by exogenous GnRH in hyperprolactinaemia, it is unlikely that a high level of prolactin by itself inhibits follicular development and ovulation.**

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Pathological hyperprolactinaemic amenorrhoea is associated with disturbances of pulsatile gonadotrophin secretion. Most authors have described a reduced LH pulse frequency which increases following treatment with bromocriptine (Moult *et al.*, 1982; Sauder *et al.*, 1984). However, Klibanski *et al.* (1984) reported a reduction in pulse frequency when hyperprolactinaemic patients were treated with bromocriptine. Although Moult *et al.* (1982) described a fairly consistent pattern of high amplitude, low frequency pulses the consensus of opinion suggests that the pattern of pulses shows marked variability between individual women. Whatever the characteristics of the disturbance of pulsatile LH secretion, it is clear that ovarian function can be restored by the exogenous administration of pulsatile GnRH (Leyendecker *et al.*, 1980; Polson *et al.*, 1986).

The mechanism underlying the disturbance of LH secretion in hyperprolactinaemic women remains unclear. There is evidence that high concentrations of prolactin increased dopamine turnover in the hypothalamus in the rat (Adler, 1986) and it has been suggested that increased

**Table 1** Details of subjects with hyperprolactinaemia

| Subjects | Age (years) | Parity | BMI ($kg/m^2$) | Time off bromocriptine (months) | PRL (mU/l) | $E_2$ (pmol/l) |
|---|---|---|---|---|---|---|
| 1 | 38 | 0+0 | 19·6 | NT | 2500 | 105 |
| 2 | 26 | 0+0 | 21·5 | 5 | 6620 | 60 |
| 3 | 44 | 2+1 | 31 | 14 | 1967 | 56 |
| 4 | 27 | 1+0 | 25 | 11 | 4030 | 100 |
| 5 | 29 | 0+0 | 22 | 7 | 7440 | 92 |
| 6 | 22 | 0+0 | 29 | NT | 2270 | <46 |
| 7* | 41 | 1+0 | 36 | NT | 5720 | 56 |
| 8* | 23 | 0+0 | 20·1 | 9 | 6850 | 110 |
| 9† | 37 | 2+0 | 21 | 3 | 2200 | 182 |
| 10† | 41 | 2+0 | 25 | NT | 1620 | 153 |

* Microadenoma on CT scan.
† Regular menses.
NT, Never treated with bromocriptine.

dopamine tone may affect the pulse generator. In the human, Quigley *et al.* (1980) suggested that the attenuated pulsatile pattern of LH release characteristic of hyperprolactinaemic patients may be due in part to an increased inhibitory effect of endogenous opioids on GnRH secretion.

In order to determine whether an increase in opioid tone may be involved in the suppression of pulsatile LH release in women with hyperprolactinaemia, we have investigated the effects of the opioid antagonist, naloxone, on the secretion of LH and FSH.

## Materials and methods

### *Subjects and sampling methods*

Ten women with hyperprolactinaemia (serum prolactin > 1500 mU/l) were recruited from the Reproductive Endocrine Clinic of the Royal Infirmary of Edinburgh. Eight of the women were amenorrhoeic and two had regular menstrual cycles (Table 1). No woman was on any medication and all had normal thyroid function tests. In those who had previously been taking bromocriptine, the treatment was stopped for at least 3 months prior to the study. All the women had normal skull X-rays but subjects 7 and 8 had evidence of microadenoma on CT scan. The two women who had regular ovulatory cycles (subjects 9 and 10) were studied in the early follicular phase of the menstrual cycle.

The study was approved by the Lothian Health Board Ethics of Medical Research Committee and informed consent was obtained from all women. The subjects were admitted to the Clinical Research Unit of the Simpson Memorial Maternity Pavilion for the study. There were no restrictions on physical activity or food intake beyond that placed by a hospital environment. Lights were switched off between 2300 and 0700 h, when they went to sleep.

**Table 2** Details of control subjects

| Subjects | Age (years) | Parity | BMI ($kg/m^2$) | PRL (mU/l) | $E_2$ (pmol/l) |
|---|---|---|---|---|---|
| 11 | 30 | 1+0 | 23 | 84 | 645 |
| 12 | 31 | 1+0 | 22 | 80 | 159 |
| 13 | 32 | 1+0 | 22·5 | <36 | 179 |
| 14 | 30 | 1+0 | 24 | 127 | 134 |
| 15 | 26 | 1+0 | 21 | 63 | 159 |
| 16 | 32 | 1+0 | 22 | 289 | 222 |
| 17 | 26 | 1+0 | 23 | 154 | 210 |
| 18 | 31 | 1+1 | 24 | 92 | 245 |
| 19 | 25 | 1+0 | 20 | 324 | 248 |

On admission to the Unit on Day 1 at 0800 h, a 20G Venflon cannula was inserted into a forearm vein and the cannula was kept patent with heparinized saline. From 0900 h, 2·5 ml sample of venous blood was collected every 10 minutes throughout 24 hours. At night during sleep, blood samples were collected through a long intravenous catheter which passed through a hole in the wall to the adjoining laboratory, allowing blood samples to be collected without disturbing the subjects' sleep.

At 0900 h on Day 2, an intravenous infusion of naloxone was commenced using an infusion pump which delivered a constant dose of 1·6 mg/hour for the next 4 hours. During the infusion, blood samples were again collected every 10 minutes for 4 hours. The plasma was separated and stored at −20°C and later assayed in batches for LH, FSH and prolactin.

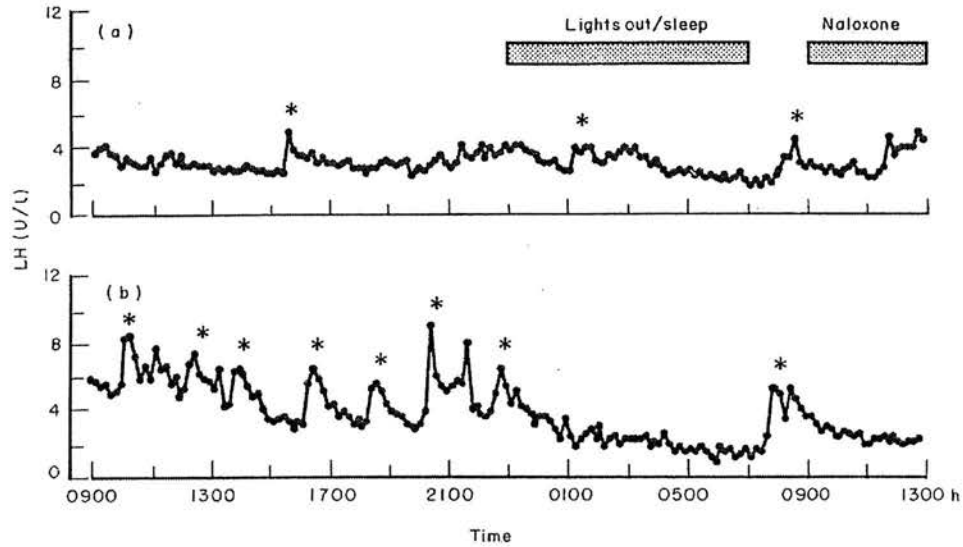


**Fig. 1** Twenty-four-hour pattern of LH secretion in two women with hyperprolactinaemic amenorrhoea. a, Subject 4 ($E_2$ 109 pmol/l; $P_4$ 1·5 nmol/l; PRL 2931 mU/l); b, subject 2 ($E_2$ 132 pmol/l; $P_4$ < 1 nmol/l; PRL 7384 mU/l).
*Statistically significant pulse of secretion.

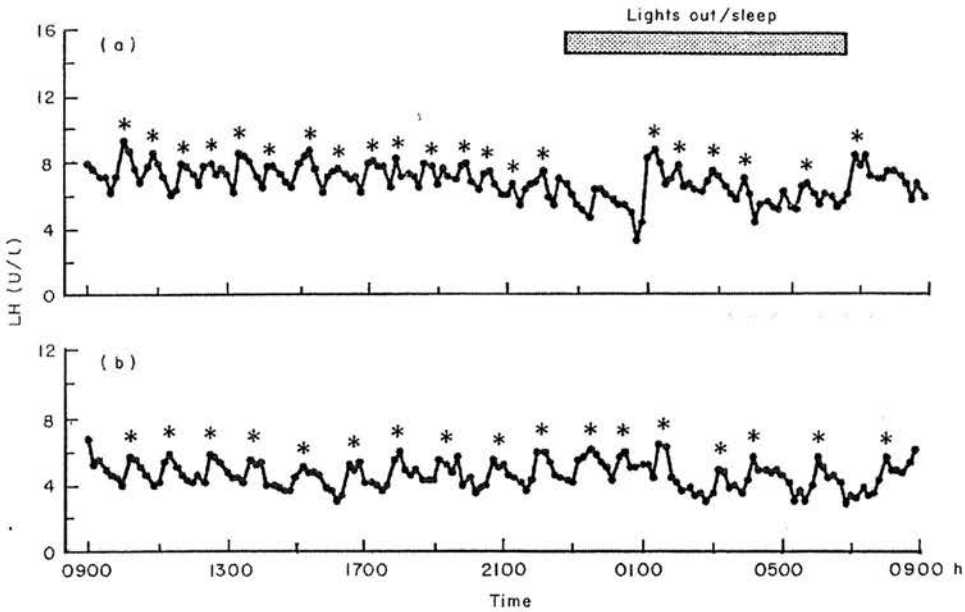


**Fig. 2** Twenty-four-hour pattern of LH secretion during the early follicular phase in two control subjects. a, Subject 11 ($E_2$ 645 pmol/l; $P_4$ < 1 nmol/l; PRL 84 mU/l); b, subject 12 ($E_2$ 159 pmol/l; $P_4$ 1·7 nmol/l; PRL 80 mU/l).
*Statistically significant pulse of secretion.

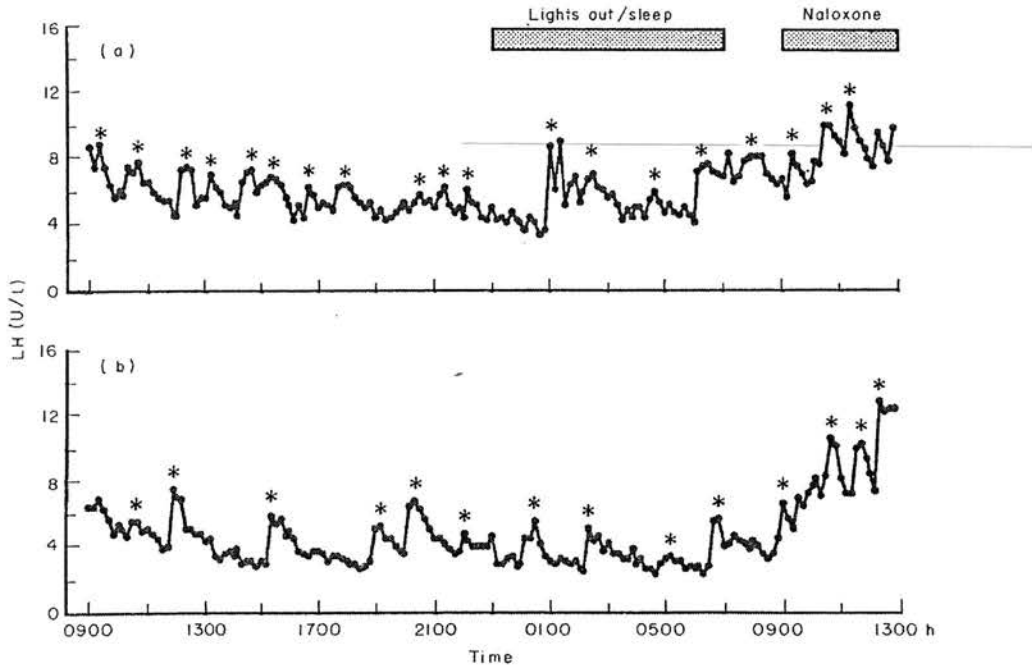


**Fig. 3** Twenty-four-hour pattern of LH secretion during the early follicular phase in two women with hyperprolactinaemia and regular menstrual cycles. a, Subject 9 ($E_2$ 665 pmol/l; $P_4$ 3·6 nmol/l; PRL 1554 mU/l); b, subject 10 ($E_2$ 257 pmol/l; $P_4$ < 1 nmol/l; PRL 1678 mU/l). *Statistically significant pulse of secretion.

*Control subjects*

Nine women (25–32 years) were studied in the early follicular phase of a normal ovulatory cycle (Table 2). Venous blood samples (2·5 ml) were collected every 10 minutes throughout the 24 hours as described above.

*Induction of ovulation by pulsatile GnRH pump*

In subject 4, treatment with the dopamine agonists bromocriptine and lisuride had failed to induce ovulation. She was then treated with gonadotrophin releasing hormone (GnRH) delivered in a pulsatile manner using a Mill Hill portable infusion pump (Sutherland *et al.*, 1984). Initially this was set to deliver at a dose of 15 μg GnRH subcutaneously every 90 minutes but this was later changed to 15 μg subcutaneously every 120 minutes and then 5 μg intravenously every 90 minutes. Ovarian activity was monitored by the daily measurement of the excretion of oestrone glucuronide and pregnanediol glucuronide in urine and the measurement twice-weekly of the concentration of oestradiol in plasma and follicular diameter and endometrial thickness by ultrasound.

*Hormone assays*

Plasma concentrations of LH and FSH were measured by radioimmunoassay as described previously (Djahanbakhch *et al.*, 1981; Hunter & Bennie, 1979) while plasma prolactin was measured in a two-site immunoradiometric assay (NETRIA, St Bartholomew's Hospital, London) (Wu *et al.*, 1990). The intra and inter-assay coefficients of variation were <8 and <11% respectively for LH, FSH and prolactin. Concentrations of oestrone glucuronide and pregnanediol glucuronide in urine were measured as described previously and corrected for the amount of creatinine in each sample (Fraser *et al.*, 1989). Plasma oestradiol and progesterone concentrations were measured by specific radioimmunoassay following diethyl ether extraction of plasma as described previously (Glasier *et al.*, 1989).

*Statistical analysis*

The data are presented as mean ± SEM except where otherwise stated. Comparisons between mean hormonal concentrations and the various parameters of pulsatile LH secre-

**Table 3** Mean values of basal LH and parameters of LH pulses among the three groups of subjects

| | Hyperprolactinaemia, amenorrhoea | Hyperprolactinaemia, regular menses | Control |
|---|---|---|---|
| Mean LH (U/l) | 5·2±1·1 | 4·8±0·8 | 5·2±0·4 |
| LH pulse frequency (per 24 h) | 4·5±2·4** | 13·5±2·5 | 17·3±0·8 |
| LH pulse amplitude (U/l) | 4·9±5·0 | 2±0·4 | 2·2±0·2 |
| LH pulse interval (min) | 498±482* | 105±15 | 83±4 |
| LH pulse area (U/l) | 339±367* | 84±2 | 62±6 |

* $P<0·05$ Significance of difference from control.
** $P<0·001$ Significance of difference from control.

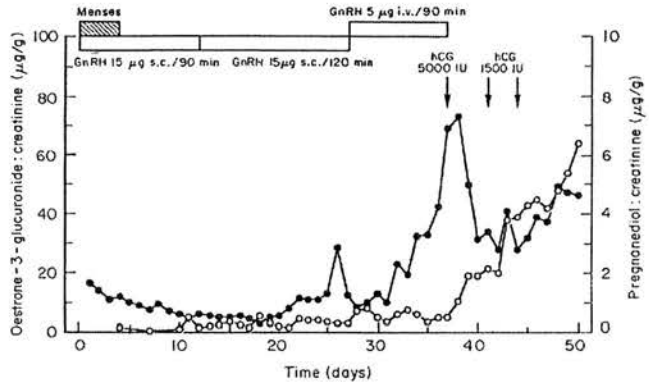


**Fig. 4** The excretion of ●, oestrone-3-glucuronide and ○, pregnanediol glucuronide in urine during the induction of ovulation with GnRH in subject 4. The route of administration was changed from subcutaneous to intravenous on day 26. 5000 IU hCG was injected on day 37 after the emergence of a single follicle 16 mm diameter.

tions were performed using Student's *t*-test. Statistically significant hormone pulses were identified using the MUNRO pulse analysis program (Zaristow Software, Haddington, Scotland, EH14 4PD) as described previously (Tay *et al.*, 1992). The mean pulse frequency, pulse amplitude, and pulse area of LH released were compared between the different groups of women.

## Results

### *individual 24-hour secretory pattern of LH*

The pattern of LH secretion was highly variable with pulse frequency ranging from 1–8 per 24 hours in individual hyperprolactinaemic women (Fig. 1). In subject 4, the secretory pattern was almost fully suppressed with only three statistically significant LH pulses detected by the MUNRO computerized algorithms over 24 hours. However, in subject 2, eight statistically significant pulses were detected over 24 hours with a mean pulse amplitude of 3·82±0·52 U/l. In contrast, LH pulses occurred much more frequently in the control women (range 14–21 per 24 hours) (Fig. 2). In subject 11, 21 LH pulses were detected over 24 hours and 17 pulses were detected in subject 12. In the two women with hyperprolactinaemia who had regular menses in spite of being hyperprolactinaemic (subjects 9 and 10), there were 16 and 11 pulses per 24 hours as shown in Fig. 3.

For each subject a single mean concentration of LH was calculated from the 145 samples collected over the 24-hour period. This value was then used to calculate an overall mean for each group of women. Although the overall mean concentration of LH in women with hyperprolactinaemia amenorrhoea was similar to controls and to women with hyperprolactinaemia and regular menses, the pattern of LH secretion was very different (Table 3). The women with hyperprolactinaemia had many fewer pulses/24 hours than women with regular cycles ($P<0·001$). However, the magnitude of each episode of secretion (as measured by the area under each LH pulse) was significantly higher in the hyperprolactinaemic women and, hence, the overall mean values were similar.

### *Induction of ovulation by pulsatile GnRH pump*

In subject 4, ovulation was induced by the administration of exogenous GnRH in a pulsatile manner. In the first cycle,

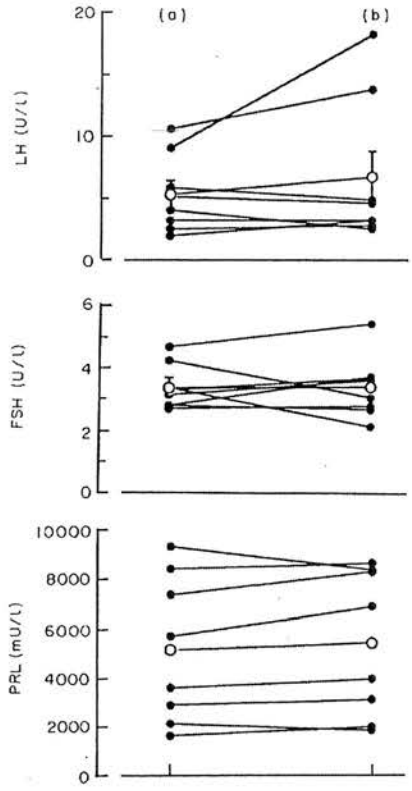


**Fig. 5** Change in mean concentration of LH, FSH and PRL in response to the infusion of naloxone among the women with hyperprolactinaemic amenorrhoea. ○, Overall mean value. a, Basal; b, naloxone.

GnRH was administered subcutaneously (15 μg/90 min), and although ovulation occurred, the luteal phase was inadequate. Following menstruation, the patient was maintained on GnRH subcutaneously with the pulse frequency reduced to every 120 minutes (Fig. 4). As the ovarian response was inadequate, the regime was changed to 5 μg GnRH intravenously every 90 minutes. A single dominant follicle (16 mm diameter) emerged within 10 days and ovulation was induced by the injection of 5000 IU of hCG. The patient became pregnant and eventually bore a healthy baby.

### *Effects of naloxone*

Despite a rise in the mean concentration of LH in one subject, there was no significant difference between the basal

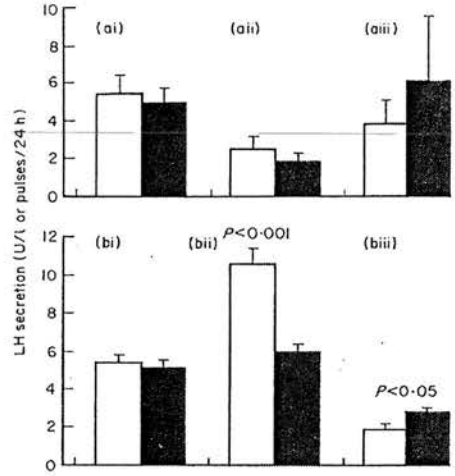


**Fig. 6** A comparison of the patterns of LH secretion during ■, sleep and □, waking hours for a, women with hyperprolactinaemia and b, control subjects. i, Mean LH; ii, LH frequency; iii, LH amplitude.

concentration of LH, FSH and PRL between 0900 and 1300 h on Day 1 and a corresponding time period 24 hours later during the infusion of naloxone (Fig. 5). Moreover, the frequency of LH pulses was similar during the same two time periods ($1{\cdot}13 \pm 0{\cdot}48$ *vs* $1{\cdot}38 \pm 0{\cdot}32$, Mann–Whitney $P$=NS).

### *Effects of light and sleep on LH secretory pattern*

The mean LH, frequency and amplitude of LH pulses during sleep, were compared with those during daylight hours in both hyperprolactinaemic amenorrhoeic and control women (Fig. 6). In neither group was there any difference in mean concentration of LH. However, in control women during sleep, there were fewer pulses ($P < 0{\cdot}001$) and their amplitude was greater ($P < 0{\cdot}05$). There was no such difference in hyperprolactinaemic women with amenorrhoea.

## Discussion

The most obvious feature of the women with hyperprolactinaemic amenorrhoea was a significant reduction in the number of LH pulses during the 24-hour period as compared with the control women or those with hyperprolactinaemia but with normal cycles. These findings confirm that LH pulses occurring at intervals of not less than every 2 hours are necessary for normal cyclical ovarian function. The fact that normal follicular development and ovulation occur if this optimum frequency is present despite abnormally high levels

of prolactin (subjects 9 and 10) suggests that high levels of prolactin are unlikely to play a direct role in suppressing ovarian activity.

It could be proposed that hyperprolactinaemic women with normal ovarian activity secrete a form of prolactin which although recognized by the radioimmunoassay is biologically inactive (Whittaker *et al.*, 1981; Fraser *et al.*, 1989). However, it is unlikely that all patients with hyperprolactinaemic amenorrhoea have biologically inactive prolactin because galactorrhoea is a common feature of this condition. The observation that follicular development, ovulation and fertility could be restored by injecting GnRH at a frequency which simulated that observed in normal women (Fig. 4) strongly supports the view that the underlying cause of the amenorrhoea is the disturbance in the pattern of secretion of GnRH which results in the abnormal secretion of gonadotrophins (Leyendecker *et al.*, 1980; Polson *et al.*, 1986). A similar conclusion concerning the cause of suppression of ovarian activity during lactation was deduced from the fact that ovulation can be induced by treating lactating women with GnRH in a pulsatile manner (Glasier *et al.*, 1986).

It has been suggested that the reduction in LH pulse frequency in women with hyperprolactinaemia is due to suppression of the activity of the GnRH neurones in association with increased secretion of endogenous opiates (Quigley *et al.*, 1980). Support for this hypothesis comes from the report that infusion of opioid antagonist (naloxone) in some hyperprolactinaemic women resulted in an increase in the concentration of LH and the frequency of LH pulses (Grossman *et al.*, 1982; Seki *et al.*, 1986). In our study, although one subject apparently showed an increase in LH pulse frequency during the infusion of naloxone, overall there was no significant rise in the secretion of LH when compared with an appropriate control period. Throughout the 24-hour period there are considerable spontaneous fluctuations in the timing of LH pulses (Figs 1 and 2). It is possible, therefore, that the apparent increase observed by Grossman *et al.* (1982) was due to spontaneous fluctuations and unrelated to the infusion of naloxone. However, Cook *et al.* (1991), demonstrated an increase in LH pulse frequency during naloxone infusion for 8 hours compared to an equivalent period during the previous day. One possible explanation for the lack of response in our study may be that the shorter duration of infusion (4 hours) was insufficient to allow adequate opioid blockade to occur. Both women who had normal ovarian cycles in spite of being hyperprolactinaemic, showed an apparent increase in LH concentration during infusion of naloxone (Fig. 3). In normal women, the concentration of LH increases following naloxone only during the late follicular and late luteal phase when the concentrations of oestradiol and progesterone are relatively high (Quigley & Yen, 1980). In lactating women, there is no increase in LH secretion after naloxone except in women who are treated with 30 $\mu$g levonorgestrel per day as a gestogen-only contraceptive (Tay *et al.*, 1993). In the monkey, the concentration of $\beta$-endorphin in the hypothalamic–hypophyseal portal blood is increased during the luteal phase of the cycle or after treatment of ovariectomized monkeys with oestradiol and progesterone (Ferin, 1983). These findings suggest, therefore, that a certain minimum level of steroid is necessary before endogenous opioid regulation of gonadotrophin secretion can be revealed by infusion of opioid antagonist. Experiments involving the infusion of naloxone in hyperprolactinaemic amenorrhoeic women treated with a gestogen would be of interest.

In control women (but not those with hyperprolactinaemic amenorrhoea), the frequency of LH pulses slowed significantly during the dark/sleep period as has been observed by others in women in the early follicular phase of the cycle (Kapen *et al.*, 1976; Crowley *et al.*, 1985). We are unable to distinguish precisely between dark and sleep, although all the women apparently slept uninterruptedly soon after the lights were switched off at 2300 h. The cause of this diurnal variation in pulse frequency is not known, although it is associated with a nocturnal rise in the secretion of prolactin and melatonin (Brzezinski *et al.*, 1988; Berga & Yen, 1990). There is no such diurnal variation in either prolactin concentration or LH pulse frequency in hyperprolactinaemic women with amenorrhoea, as shown in our study and by others (Klibanski *et al.*, 1984). In rhesus monkeys the onset of darkness is associated with a striking reduction in the activity of hypothalamic GnRH neurones as reflected by recording of multi-unit activity by hypothalamic electrodes (O'Byrne *et al.*, 1991).

Further experiments exploring the relations between diurnal rhythms of prolactin, LH, melatonin and hypothalamic electrical activity, may help explain the pathogenesis of hypothalamic hyperprolactinaemic amenorrhoea.

**Acknowledgements**

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# INDUCTION OF OVARIAN ACTIVITY BY PULSATILE INFUSION OF LHRH IN WOMEN WITH LACTATIONAL AMENORRHOEA

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SUMMARY

Four fully breast-feeding women at 6 weeks post partum were injected with LHRH (0·1 μg/kg) every 94 min by pulsatile infusion pump. While follicular development occurred in all women, and evidence of luteinization was apparent in three out of four, normal ovulation and luteal function did not occur. This suggests that a simple disturbance in the pulsatile pattern of LHRH secretion may not, in itself, be enough to explain the suppression of ovarian activity during lactation.

The mechanism by which breast-feeding delays the resumption of ovarian activity post partum remains unclear. Disturbances in the pattern of LH secretion may be, however, instrumental in maintaining lactational amenorrhoea (McNeilly, 1979; Glasier *et al.*, 1983). Recently we have demonstrated that during complete suppression of ovarian activity there is a reduction in the frequency and amplitude LH pulses in 76% of breast-feeding women studied (Glasier *et al.*, 1984).

Longitudinal studies have demonstrated that the resumption of ovarian activity is associated with a decrease in suckling activity and an associated decrease in prolactin concentrations (McNeilly *et al.*, 1980; Howie *et al.*, 1981). The elevated concentrations of prolactin in peripheral blood may be instrumental in maintaining amenorrhoea post partum, acting either at the level of the hypothalamus or directly at the ovary, or may simply be an index of the level of hypothalamic activity during suckling. In order to establish whether the restoration of a normal pulsatile pattern of LHRH secretion, in the presence of hyperprolactinaemia, would result in normal ovulation we have studied four breast-feeding mothers treated with LHRH administered by pulsatile infusion pump.

## SUBJECTS AND METHODS

Four women aged 22–33 years, three primigravid, were recruited from the post-natal

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wards of the Simpson Memorial Maternity Pavilion. None was using any hormonal form of contraception. From 4 weeks post partum, and for the duration of the study, ovarian activity was monitored by the estimation of oestrogen: creatinine and pregnanediol: creatinine ratios, in daily early morning specimens of urine (EMU) which were stored at −20°C and assayed in batches. Once the study was completed EMUs were also assayed for LH, the samples from each individual subject being assayed in a single batch. All mothers kept a record of the frequency and duration of suckling episodes, and of any supplementary feeds, either bottled milk or solids, given. Night feeds, occurring between midnight and 0600 h, were recorded separately. Records of any menstrual bleeding were kept. At between 6 and 7 weeks post partum the women were fitted with a Mill Hill portable infusion pump (Sutherland *et al.*, 1984) set to deliver 0·1 μg/kg LHRH in saline solution in a bolus of 40 μl every 94 min. The pumps were worn on a belt around the waist and the LHRH solution delivered subcutaneously into the anterior abdominal wall. For the first or last week of treatment all four women received only normal saline solution, 40 μl every 94 min, as a placebo.

Once each week follicular diameter was measured by ultrasound and 5 ml samples of blood were collected every 15 min for 4 h. After each sample the cannula was flushed through with a heparinized saline solution (5000 units heparin in 100 ml saline) and the first 1 ml of the next sample was discarded. No restraint on activity was made during this 4 h period, and breast-feeding took place on demand. Blood samples were centrifuged at 4500 r/min for 20 min and stored at −20°C until assayed for LH, FSH and prolactin.

The study had the approval of the Reproductive Medicine Ethical sub-committee of the South Lothian District Health Authority.

### *Assay methods*

Urinary excretion of total oestrogen was measured fluorimetrically (Brown *et al.*, 1968) and pregnanediol was determined by gas-liquid chromatography (Chamberlain & Contractor, 1968). Creatinine was measured by auto analyser and the steroid: creatinine and LH: creatinine ratio determined (Metcalf & Livesey, 1979). Both urinary LH and serum PRL were measured in duplicate by RIA (McNeilly & Hagen, 1974). Interassay coefficient of variation (between 80 and 20% $B/B_0$) was 6·5% and interassay coefficient of variation 9·3% for LH.

All samples for prolactin were measured in the same assay with an intra-assay coefficient of variation of 5·8%. Serum LH and FSH were measured by RIA (Hunter & Bennie, 1978). The intra-assay coefficients of variation were 10% and 9% and the interassay coefficients of variation (16% and 15%) for LH and FSH respectively. Oestradiol and progesterone were measured by RIA (Scaramuzzi *et al.*, 1975; Bäckström *et al.*, 1982). Sensitivities were 5 pg/ml for oestradiol and 140 pg/ml for progesterone. Interassay and intra-assay coefficients of variation were 13% and 9% and 15% and 8% for oestradiol and progesterone respectively.

### *Statistical analysis*

Student's *t*-test for paired observations were used throughout.

## RESULTS

### *Pattern of ovarian activity*

Daily oestrogen:creatinine, pregnanediol:creatinine and LH:creatinine ratios, together with suckling frequencies are shown for one woman (Mrs A) in Fig. 1. Within 48 h of starting LHRH, urinary oestrogen excretion had increased more than fivefold compared with the mean of the preceding 14 d and remained elevated for 8 d. A surge of urinary LH occurred 4 d after the start of LHRH treatment. Ultrasound scans at 1 and 7 d after starting treatment also showed evidence of some follicular development. There was a rise in urinary pregnanediol excretion but the maximum pregnanediol:creatinine ratio reached on the 14th day after starting treatment was only 0·93 and serum progesterone never rose above 1 nmol/l, suggesting that ovulation did not occur. Menstrual bleeding occurred 10 d after starting LHRH. After 14 d LHRH treatment was stopped and the pulsatile infusion of saline alone continued for 7 d. Ovarian activity remained suppressed

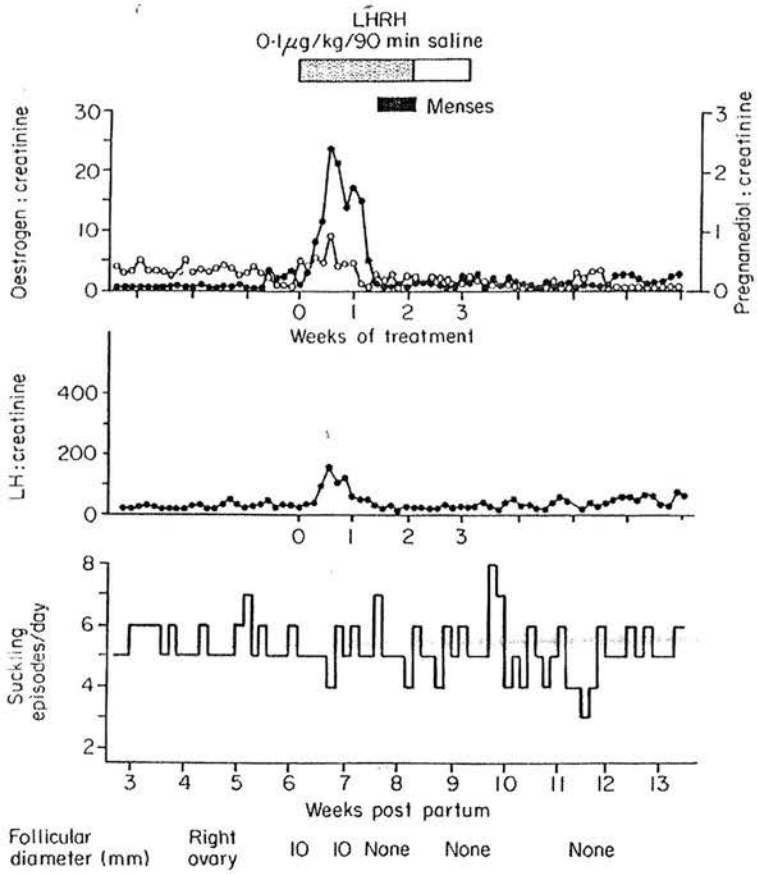


Fig. 1. Subject A (Mrs A, para 2+0; weight 55 kg, 6 weeks post partum). Daily urinary oestrogen:creatinine (●——●) and pregnanediol:creatinine ratios (○——○) together with suckling frequency (□) before, during and after LHRH administration. Follicular diameter is shown at the bottom of the figure. Follicular development was apparent in response to LHRH administration but pregnanediol:creatinine ratios did not reach a level of one. Solid feeds were introduced in the thirteenth post partum week.

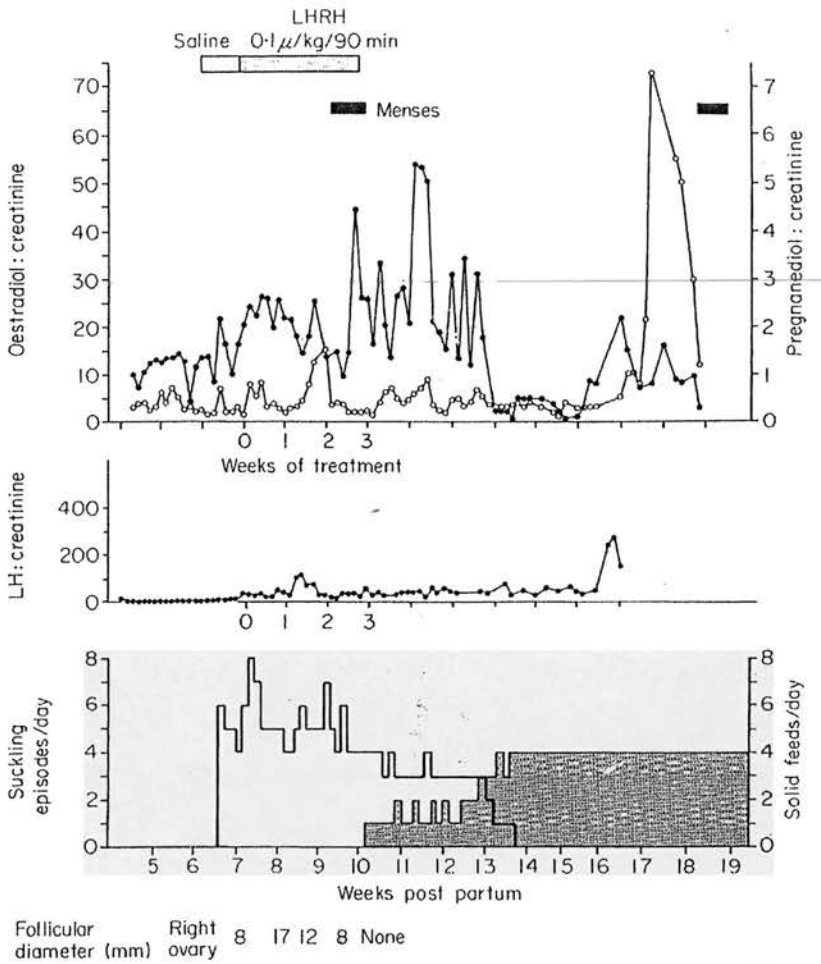


Fig. 2. Subject B (Mrs B, para 2+0; weight 60 kg, 7 weeks post partum). LHRH administration resulted in a rise in urinary oestrogen:creatinine (●——●) ratio and ultrasound evidence of follicular development. Follicular diameter is shown at the bottom of the figure. A rise in pregnanediol:creatinine ratio (○——○) suggested that luteinization had occurred. Suckling frequency (□) fell and solid feeds (■) were started from 10 weeks post partum resulting in a normal ovulatory cycle at around 17 weeks.

during this time and for a further 4 weeks of the study, during which time breast-feeding continued unsupplemented.

Mrs B (Fig. 2) showed a sustained rise in oestrogen excretion accompanied by ultrasound evidence of follicular development until 14 d after starting LHRH infusion, when a fall in oestrogen and pregnanediol concentration preceded the onset of menstruation on day 15. An LH surge occurred on days 8 and 11, followed by a rise in urinary pregnanediol concentration on day 11. Maximum pregnanediol:creatinine ratio of 1·54 occurred on day 14 with serum progesterone of 1·12 nmol/l. The follicular phase lasted 10 d and luteal phase (from the first rise in pregnanediol to menstruation) lasted only 4 d. Supplementary feeding started as soon as LHRH treatment was stopped at 10 weeks post partum, and oestrogen:creatinine ratio remained elevated for a further 3

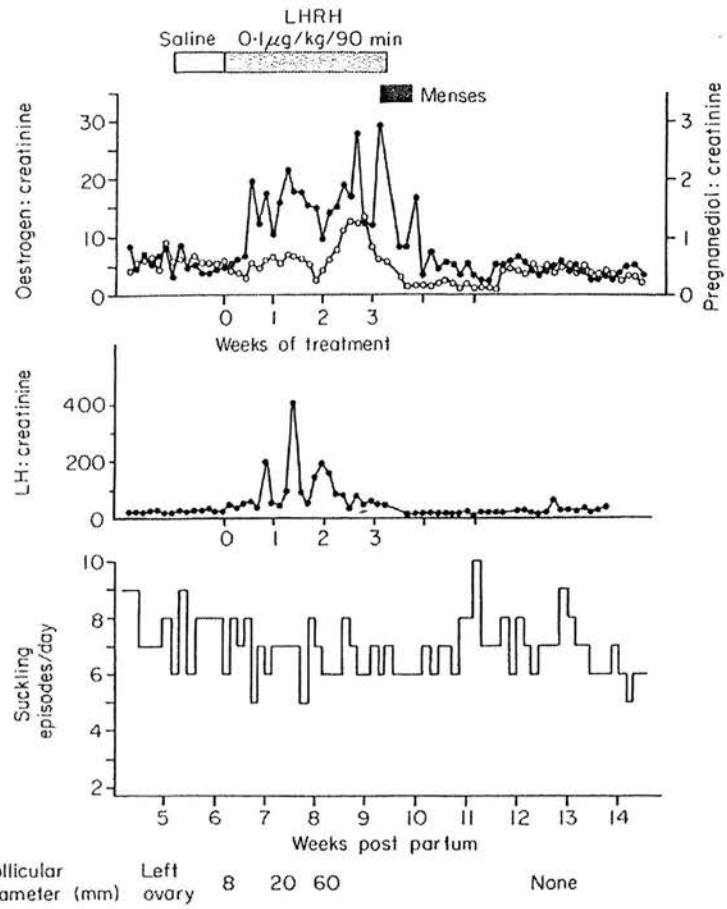


Fig. 3. A more prolonged rise in urinary oestrogen:creatinine ratio (●——●) is seen in the case of Subject C (Mrs C, para 1+0; weight 72 kg, 6 weeks post partum) with a more marked rise in pregnanediol:creatinine ratio (○——○) in response to LHRH. Full breast feeding (□) continued unsupplemented throughout the study.

weeks. An apparently normal spontaneous ovulatory cycle occurred at 17 weeks post partum.

A similar sustained rise in oestrogen excretion with ultrasound evidence of follicular development was seen in a third woman (Mrs C) (Fig. 3). Before the start of treatment an 8 mm diameter follicle was present which persisted and reached a diameter of 60 mm 17 d after starting treatment. This increase in follicle diameter was accompanied by a sustained increase in oestrogen:creatinine and was associated with three peaks of urinary LH. The final increase in LH on day 14 of treatment was followed by a rise in pregnanediol:creatinine ratio (maximum 2·71) on day 15. Serum progesterone on day 14 was 7·61 nmol/l and menstruation occurred on day 22, giving a follicular phase of 15 and a luteal phase of 5 d. After stopping treatment with LHRH, ovarian activity suppressed again and Mrs C was still partially breast-feeding at 42 weeks post partum. The dominant follicle, which reached 20 mm diameter 10 d after starting treatment, persisted and reached a diameter of 60 mm 7 days later.

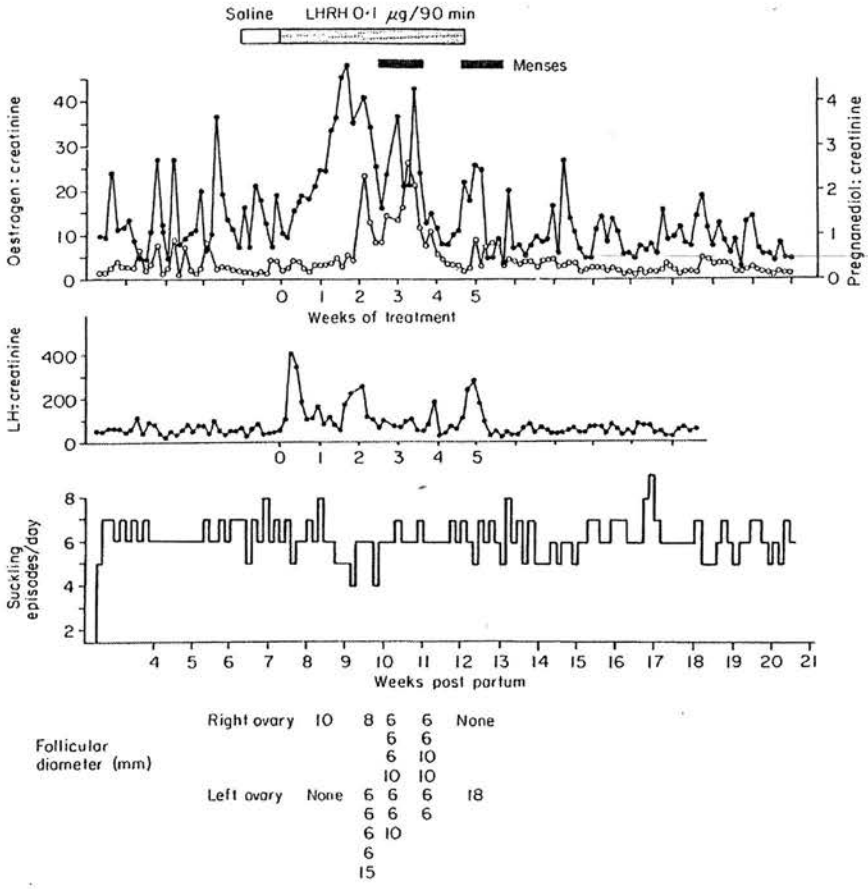


Fig. 4. With Subject D (Mrs D, para 1+0, 54 kg). LHRH resulted in a marked rise in urinary oestrogen:creatinine (●——●) ratios, large numbers of small follicles were seen on ultrasound scan and a marked rise in urinary pregnanediol:creatinine (○——○) ratio 14 d after starting LHRH was followed by menstruation (■). A second rise in pregnanediol:creatinine ratio suggested luteinization of a second follicle. Suckling frequency (□) and frequency of solid feeds (■) are shown in the lower part of the figure.

A rise in urinary pregnanediol:creatinine ratio (maximum 2·33) occurred on the 14th day after starting LHRH in the fourth woman (Mrs D) (Fig. 4), four days later menstrual bleeding occurred coincidental with a fall in pregnanediol excretion. A second rise in pregnanediol:creatinine suggesting luteinization of a second follicle, occurred two days later and was sustained (maximum 2·61) for a further 9 d despite continued vaginal bleeding. A marked increase in urinary LH concentration occurred immediately LHRH treatment began and two further 'surges' occurred, perhaps coincidental with luteinization of a second and even third follicle. LHRH treatment was given for a total of 34 d, after which Mrs D received subcutaneous saline for 7 d. Ovarian activity remained suppressed for a further 8 weeks of study, during which Mrs D continued unsupplemented breast-feeding.

Table 1. Mean serum prolactin, oestradiol, progesterone, LH and FSH together with the frequency and amplitude of pulses of secretion of LH and FSH and LH:FSH ratio in relation to weeks of LHRH treatment

| | Before treatment | Weeks of LHRH | | | | After treatment |
|---|---|---|---|---|---|---|
| | | 1 | 2 | 3 | 4 | |
| Number | 4 | 4 | 3 | 3 | 1 | 2 |
| Prolactin (mU/l) | 1611±359 | 1195±82 | 2046±789 | 1174±401 | 1071±290 | 631±32 |
| Oestradiol (pg/ml) | 52±9 | 135±28 | 112±32 | 79±36 | 65 | 43±5 |
| Progesterone (nmol/l) | 0·4±0·1 | 0·3±1·5 | 3·4±1·5 | 1·4±0·9 | 0·99 | 0·3±0·03 |
| LH (U/l) | 2·7±0·5 | 5·3±1·2 | 6·9±2·3 | 4·1±1·4 | 3·8±0·2 | 2·6±1·0 |
| FSH (U/l) | 7·2±0·6 | 4·9±1·2 | 7·3±2·0 | 4·4±0·8 | 5·6±0·3 | 6·0±0·6 |
| LH pulse amp (U/l) | 1·7±0·9 | 5·7±2·7 | 2·7±0·8 | 2·0±0·8 | 1·5±0·3 | 3·2±0·3 |
| LH pulse freq./4 h | 1±0·4 | 1·5±0·3 | 1·8±0·2 | 1·7±0·3 | 3·0 | 1·5±0·4 |
| FSH pulse amp (U/l) | 2·3±0·2 | 1·7±0·3 | 1·4±0·6 | 1·5 | 1·6 | 1·3 |
| FSH pulse freq./4 h | 0·8±0·2 | 1·8±0·2 | 0·5±0·3 | 0·3±0·3 | 2·0 | 1·3 |
| FSH:LH | 3·0:1±1·0 | 1·3:1±0·6[b] | 1·2:1±0·2[b] | 1·3:0·2[a] | 1·5:1 | 3·6:1±1·6 |

Significance of difference from suppressed (paired *t*-tests): [a]$P<0·05$; [b]$P<0·01$.

### *Patterns of gonadotrophin secretion*

The mean concentrations, together with the frequency and mean amplitude of pulses of secretion of both LH and FSH during serial blood sampling episodes are shown in Table 1. The FSH:LH ratios and mean concentrations of prolactin are also shown and results are subdivided according to weeks of treatment. In all cases, mean concentrations of LH were higher during LHRH administration than when ovarian activity was suppressed by unsupplemented breast-feeding, although this did not reach statistical significance. There was also a tendency for FSH concentrations to fall as oestrogen levels increased, in response to LHRH. The increase in LH and decrease in FSH concentrations was reflected by a marked fall in the FSH:LH ratio during LHRH administration ($P<0·01$; after 1 and 2 weeks of treatment; and $P<0·05$ after the third week). The patterns of gonadotrophin secretion during serial sampling episodes in two women are shown in Fig. 5. On most occasions a pulse of exogenous LHRH was followed by a pulse of LH resulting in an increased LH pulse frequency, clearly seen in the case of Mrs D (upper figure) in whom the FSH:LH ratio tended towards unity during LHRH administration. During unsupplemented breast-feeding, and despite the suppression of ovarian activity, one woman (Mrs A—lower figure) had higher concentrations of LH and a more markedly pulsatile pattern of LH secretion than that characterizing the other three women. In this case LHRH administration did not result in a normalization of the FSH:LH ratio.

### *Patterns of prolactin secretion and suckling behaviour*

Mean serum prolactin concentrations were higher than the normal range for non-lactating women throughout the study. An acute increase in prolactin secretion occurred in response to suckling in all women. There was no significant difference between mean prolactin concentration before or at the end of LHRH administration and there appeared

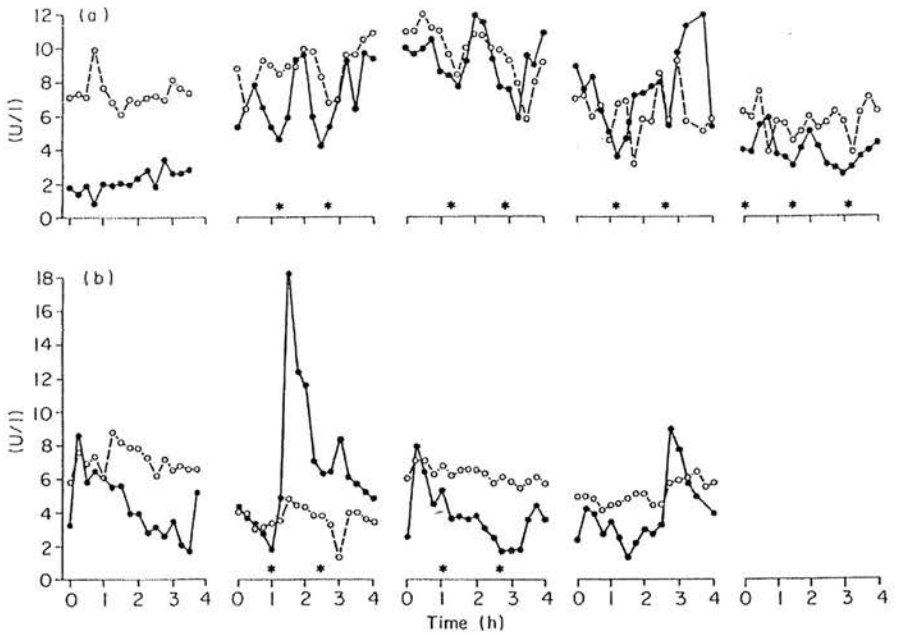


Fig. 5. Patterns of LH (●——●) (U/l) and FSH (o– – –o) (U/l) during serial blood sampling episodes in the women: (a) Mrs C; (b) Mrs A.

to be no direct relationship between either the degree of hyperprolactinaemia or the frequency and duration of suckling and whether or not ovulation occurred or the adequacy of the resultant luteal phase.

## DISCUSSION

The pulsatile administration of LHRH resulted in follicular development in all four women, with evidence of luteinization occurring in three out of the four, despite full breast-feeding and hyperprolactinaemia. In the three women who continued full breast-feeding, ovarian activity resuppressed and amenorrhoea persisted for at least 36 weeks post partum. The duration of the follicular phase and length and adequacy of the luteal phase was extremely variable between the four women.

The dose, frequency and site of administration of LHRH was identical to that used successfully to induce ovulation in women with hypothalamic and hyperprolactinaemic amenorrhoea (Glasier *et al.*, in preparation). Each pulse of exogenous LHRH resulted in a pulse of endogenous LH secretion, such that LH pulse amplitude and frequency, in at least two out of the four women (Mrs A and Mrs C), during the follicular phase was compatible with that characterizing the normal follicular phase (Bäckström *et al.*, 1982).

In all four women an increase in urinary LH excretion was identified just before an increase in urinary pregnanediol concentration, and in two women an increase in LH concentration and in LH pulse amplitude occurred at this time. Thus, despite maintaining a constant frequency and amplitude of LHRH pulses, a mid-cycle surge of LH occurred indicating that the positive feedback effect of oestrogen is present. Furthermore, a fall in

FSH secretion, presumably in response to the secretion of oestrogen and inhibition by the developing follicle suggests that negative feedback mechanisms were also intact.

In the three women who appeared to ovulate in response to LHRH, the most striking feature was a fall in the FSH:LH ratio towards unity. Wildt *et al.* (1981) showed that changes in the frequency of LHRH stimulation to hypophysectomized rhesus monkeys altered not only the absolute levels of FSH and LH in the circulation, but also the ratio of one to another. It has been suggested that alterations in the ratio of FSH:LH may be involved in the pathophysiology of some amenorrhoeic states (Leyendecker, 1979; Yen, 1980). Furthermore, the onset of ovarian activity at puberty (Burr *et al.*, 1970) and the resumption of menstrual cycles after post partum amenorrhoea in rhesus monkeys (Plant *et al.*, 1980) has been shown to be associated with a change in the FSH:LH ratio towards unity. Our observations may therefore explain why one woman (Mrs A), in whom an abnormal FSH:LH ratio persisted despite LHRH administration, failed to ovulate, and may also provide indirect evidence that a change in the FSH:LH ratio, as a result of an abnormal pattern of endogenous LHRH secretion, may be instrumental in maintaining lactational infertility.

Whether prolactin itself is merely a marker of suckling or whether it is directly involved in the mechanisms underlying amenorrhoea associated with breast-feeding remains unresolved. If suckling acted simply by altering the pattern of LHRH secretion in breast-feeding women, one might expect the administration of a physiological regimen of LHRH to result in normal ovulation, yet all the woman had an abnormal luteal phase. Naturally occurring first cycles in both bottle- and breast-feeding women post partum are often anovulatory or characterized by a deficient luteal phase (McNeilly *et al.*, 1982c; Poindexter *et al.*, 1983). The delay in the resumption of normal ovulatory cycles in bottle-feeding women depends mainly, if not exclusively, on the time taken for recovery of the hypothalmo-pituitary axis from the suppressive effects of pregnancy. The breast-feeding women were treated at 6 weeks post partum when these effects might still be expected to be in force. Had LHRH administration continued beyond first menstruation, subsequent cycles may have been characterized by normal ovulation. Ishizuka *et al.* (1984) has suggested that post partum hypogonadotropism may be accounted for by the extension from pregnancy of increased hypothalamic opioid inhibition of LHRH secretion. If this were the case, the restoration of a normal pulsatile pattern of LHRH should result in normal ovulation, unless coexistent high circulating levels of prolactin were acting directly at the ovary to influence ovarian function (McNeilly *et al.*, 1982a, b).

In conclusion, sustained ovarian activity can be induced in fully breast-feeding women by the restoration of a pulsatile pattern of LHRH which induces normal ovulatory cycles in hypogonadotrophic and hyperprolactinaemic women, principally by restoring a normal FSH:LH ratio. However, normal ovulation does not occur in breast-feeding women in spite of continued LHRH administration. Whether prolactin is involved in suppressing ovarian responsiveness directly, or whether as yet inadequately defined deficiencies in LH secretion, in particular around the preovulatory surge, are responsible for the failure of normal luteal function, remains to be investigated.

ACKNOWLEDGEMENTS

We would like to thank Dr I. A. Sutherland, Engineering Department, National Institute for Medical Research, Millhill, London for making the pulsatile pumps available to us. The assistance of Sister Ann Cook and Jenny Gray is gratefully acknowledged.

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# EVIDENCE FOR GONADAL DESENSITIZATION AFTER PULSATILE THERAPY IN WOMEN WITH AMENORRHOEA?

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SUMMARY

Sixteen women with primary and secondary amenorrhoea were treated with pulsatile GnRH administered subcutaneously. Ovulation was successfully induced in 6/8 women with hypogonadotrophic hypogonadism; and in 2/2 women with idiopathic hyperprolactinaemia; but in only 3/6 women with amenorrhoea associated with an elevated LH:FSH ratio. Using serial blood sampling, we were unable to demonstrate the establishment of a physiological pattern of gonadotrophin secretion in the presence of an apparently normal menstrual cycle. Nor did we observe a consistent relationship between injection of GnRH and the resultant gonadotrophin response. A reduction or total cessation of both pituitary and gonadal sensitivity to GnRH was observed in four women. Possible reasons for these findings are discussed.

Since the late 1970s, GnRH given in a pulsatile manner has been used to treat a variety of amenorrhoeic states. Most studies report excellent results in women with hypogonadotrophic amenorrhoea (Mason *et al.*, 1984; Santoro *et al.*, 1986) and in hyperprolactinaemic amenorrhoea (Abdulwahid *et al.*, 1985; Polson *et al.*, 1986). Results of induction of ovulation with GnRH in women with polycystic ovary syndrome (PCO) are variable and often disappointing (Adams *et al.*, 1985; Burger *et al.*, 1985). In our hands some women prove difficult to treat, GnRH failing to induce ovulation or even in some cases follicular development. We report our findings in a group of 16 patients with amenorrhoea in whom we have carried out intensive monitoring, both of patterns of secretion in response to GnRH and of ovarian activity.

## PATIENTS AND METHODS

### *Patients*

Sixteen women presenting with primary (2) or secondary (14) amenorrhoea, 14 of whom wished to conceive, were admitted to the study. Eight women, including two with primary

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amenorrhoea, had hypogonadotrophic amenorrhoea with basal LH concentrations less than 1·5 U/l (group A); six had gonadotrophins within the normal range and an elevated LH:FSH ratio (group B); and in two diagnosis of idiopathic hyperprolactinaemia had been made (group C). The means and ranges of age, body mass index and basal gonadotrophin concentrations, together with basal PRL concentration, are shown in Table 1.

### *Treatment*

GnRH (HRF Ayerst, South Way, Andover, Hants 0·5 mg ampoule) was administered by automatic portable pulsatile infusion pump (Sutherland *et al.*, 1984) with a pulse interval of 90 min. The dose varied from 0·1 μg/kg/pulse to 0·4 μg/kg/pulse, and route of administration was s.c. in all but one patient who received GnRH intravenously. Each pulse was contained in a volume of 40 μl. The site for injection used was the s.c. tissue of the lower abdominal wall and was changed approximately every 4 d. All patients were started on a dose of either 0·1 or 0·2 μg/kg/GnRH and maintained on this dose for at least 21 d, if no response or an inadequate response was observed the dose was increased in 0·1 μg/kg increments, each incremental dose being maintained for at least 21 d.

### *Monitoring*

The response to treatment was assessed by frequent (daily or three times weekly) estimations of total oestrogen and pregnanediol to creatinine ratios in early morning urine specimens (EMU). Blood samples were taken once each week for the measurement of LH, FSH and, where relevant, PRL.

Follicular development was monitored using pelvic ultrasound scans once each week and more often in the late follicular phase of the cycle.

### *Serial sampling techniques*

In 13 of the women a serial sampling episode was carried out once each week to determine the pattern of secretion of LH and FSH in response to the pulsatile infusion of GnRH. An indwelling cannula was inserted into a forearm vein at 0845 h and 5 ml of venous blood taken every 15 min for 4 h. After each sample, the cannula was flushed through with heparinized saline (5000 IU of heparin per 100 ml normal saline) to prevent clotting, and the first 1 ml of the following sample was discarded to avoid dilution. Plasma was separated by centrifugation and stored at −20°C until assayed for gonadotrophins.

### *Hormone assays*

Urinary excretion of total oestrogen was measured fluorimetrically (Brown *et al.*, 1968), and pregnanediol was determined by gas-liquid chromatography (Chamberlain & Contractor, 1968). Creatinine was measured by autoanalyser and the steroid:creatine ratio determined (Metcalf & Livesey, 1979). FSH and LH were measured by the specific double-antibody RIA methods of Hunter & Bennie (1979). The intra-assay coefficients of variation were 10% and 9% and the interassay coefficients of variation 16% and 15% for LH and FSH, respectively. The sensitivity of the systems were 0·3 U/l for both FSH and LH. Results were expressed in U/l of the appropriate standards obtained from the

Table 1. Mean values and ranges for age, body mass index, basal gonadotrophins and prolactin for women in group A (hypogonadotrophic amenorrhoea), group B (increased LH:FSH ratio) and group C (idiopathic hyperprolactinaemia—shown as individual patients)

| Subjects | Age (years) | BMI | LH (U/l ± SEM) | FSH (U/l ± SEM) | PRL (mU/l) |
|---|---|---|---|---|---|
| Group A | 29·3 | 20·5 | 1·2 ± 0·2 | 3·1 ± 0·6 | 175 ± 39 |
| ($n$ = 8) | Range 24–35 | Range 18·5–24·8 | Range 0·7–1·5 | Range 2·0–5·1 | 82–354 |
| Group B | 27·8 | 23·3 | 15·2 ± 2·9 | 4·7 ± 0·9 | 259 ± 50 |
| ($n$ = 6) | Range 26–33 | Range 20·1–27·1 | Range 9·9–21·4 | Range 3·7–6·3 | 99–456 |
| Group C | 20 | 23·4 | 6·0 | 7·7 | 2281 |
| | 30 | 22·0 | 6·4 | 7·8 | 1516 |

National Institute of Biological Standards and Control, Holly Hill, London (LH: MRC 68/40 77 IU/ampoule; FSH: MRC 69/104 10 IU/ampoule).

PRL was measured by the double-antibody RIA described by McNeilly & Hagen (1974) using MRC standard 75/504 (10 IU/ampoule). Results are expressed in mU/l. The sensitivity of the assay was 18·5 mU/l and the inter- and intra-assay coefficients of variation were 17% and 10%, respectively.

To reduce variation, plasma samples obtained from each woman on all occasions were assayed as a single batch in each RIA.

## RESULTS

The response to treatment of the patients in groups A and B is summarize in Table 2. On the basis of steroid concentrations in early morning urine specimens and ultrasound evidence of follicular development, we have divided the results of treatment into five categories. (a) Patients with no rise in oestrogen excretion above the mean baseline value observed during the 21 d before starting treatment, and in whom no follicles of greater than 8 mm in diameter were demonstrated by ultrasound, were said to have shown no response to GnRH. (b) When urinary oestrogen excretion increased to a level of more than 100% of baseline and greater than 10 $\mu$g/mg creatinine/24 h on three consecutive days, and there was ultrasound evidence of follicles $>8$ mm in diameter, follicular development (FD) was said to have occurred and (c) if menstruation followed, but the criterion below for ovulation was not met, the response was described as an anovulatory cycle (AC). (d) Ovulation was said to have occurred when a rise in oestrogen excretion was followed by an increase in pregnanediol:creatinine ratios $>1·0$ mg/g creatinine/24 h, but was deemed inadequate if the luteal phase lasted less than 10 d, or if pregnanediol:creatinine ratio was $<2$ mg/g creatinine/24 h. In a number of women an initial increase in oestrogen excretion was followed by a return to levels equal to or less than the mean baseline value, if this pattern persisted for more than 10 d it was termed desensitization.

In group A, six out of eight women ovulated on a dose of either 0·1 or 0·2 $\mu$g/kg GnRH administered s.c. One women (patient F) failed to respond at all to s.c. GnRH, but ovulated in response to both 0·1 and 0·2 $\mu$g/kg doses given intravenously. Two women in group A desensitized, one following ovulation (patient A), and a second following a short-lived episode of follicular development (patient C).

In group B ovulation was induced in three women with a dose of 0·1 μg/kg GnRH; one woman failed to respond; and in two patients desensitization occurred. One patient in group B (patient K, Fig. 1) ovulated immediately GnRH treatment was started having previously been amenorrhoeic for 3 years. Following menstruation and despite continuing treatment with the same dose of GnRH for 6 weeks, ovarian activity appeared to be completely suppressed. On cessation of treatment the patient ovulated spontaneously, conceived and proceeded to a full term delivery of a healthy infant.

Both women with idiopathic hyperprolactinaemia ovulated in response of 0·1 μg/kg GnRH administered s.c. The results of one woman are shown in Fig. 2.

### *Serial sampling results*

The results of six serial sampling episodes for one woman with hypogonadotrophic amenorrhoea (patient A) are shown in Table 3 and in Fig. 3. The patient weighed 48 kg (ponderal index = 18·5). Serial sampling was carried out on two occasions before treatment was started, mean serum LH concentration during these two episodes was 1·5 ± 0·1 SEM U/l and mean basal FSH 2·5 ± 0·1 SEM U/l giving an LH:FSH ratio of 0·58. Using the definition of a pulse as described elsewhere (Glasier *et al.*, 1984), only one pulse of LH secretion could be identified during one of these sampling periods and none in other. The patient was treated for 42 d with s.c. GnRH at a dose of 0·1 μg/kg/90 min. During the first 28 d, urinary oestrogen:creatinine ratios rose to a maximum of 23 μg

Table 2. Response to treatment by dose of the patients in group A and group B

| Patient | 0·1 (μg/kg) | 0·2 (μg/kg) | 0·3 (μg/kg) | 0·4 (μg/kg) |
|---|---|---|---|---|
| A | FD | Ovulated + desen | Desen | — |
| B | FD | Ovulated | — | — |
| C | — | Desen | Desen | — |
| D | Ovulated × 3<br>Pregnant | — | — | — |
| E | Anovulation | — | — | — |
| | Ovulation + preg | — | — | — |
| F | No response<br>Ovulated IV | No response<br>Ovulated IV | No response | No response |
| G | — | Ovulated* | Ovulated | — |
| H | — | Ovulated | — | — |
| Group B | | | | |
| I | Ovulated* | | | |
| J | No response | No response | | |
| K | Ovulated + desen | — | | |
| L | FD + desen | — | | |
| M | Ovulated<br>Pregnant | | | |
| N | — | No response | No response | No response |

FD, Follicular development; desen, desensitized; preg, pregnancy; dev, development.

* Inadequate or short luteal phase.

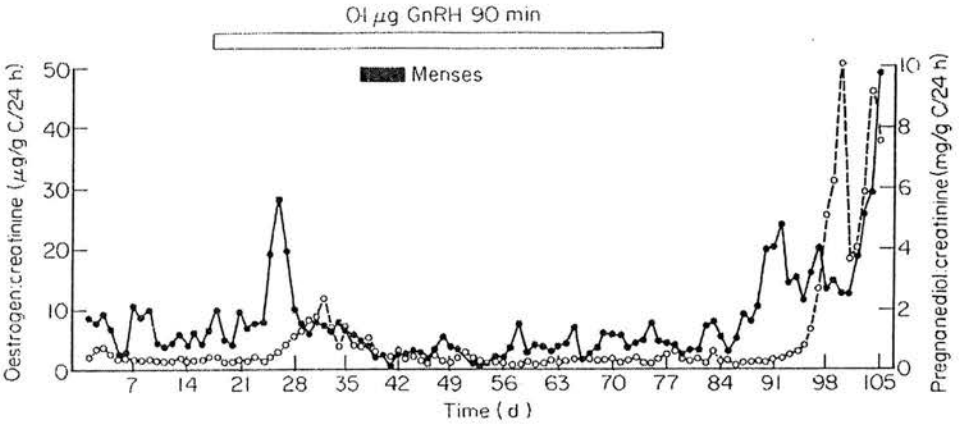


Fig. 1. Daily oestrogen:creatinine (C) ratios (●——●) and pregnanediol:creatinine ratios (○ – –○) for one woman in group B (patient K). GnRH was administered from day 19, ovulation occurred followed by menstruation (▣) 12 d after the first rise in P:C ratio. Ovarian activity remained suppressed for 6 weeks until GnRH treatment was terminated when spontaneous ovulation resulting in a pregnancy occurred.

oestrogen/g creatinine and ultrasound scans showed the presence of multiple small follicles. Thereafter oestrogen:creatinine ratios fell to a level consistently below 5 μg oestrogen/g creatinine despite continued treatment with GnRH and the continued presence of multiple small follicles. Seven days after the start of treatment, levels of LH and FSH had both increased to a mean of 2·1 and 4·4 U/l, respectively, although the ratio of LH to FSH, however, remained unchanged at 0·5:1. After 21 d of treatment, serial sampling showed a further increase in mean LH concentrations to 4·1 U/l and a normalization of the LH to FSH ratio to 1·2:1. Pulse frequency had fallen, with, at 35 d, no pulses of LH secretion identifiable in response to GnRH. After 42 d the dose of GnRH was doubled to 0·2 μg/kg/90 min and this resulted in an apparently normal ovulatory cycle with a luteal phase lasting 13 d followed by menstruation. In the mid-follicular phase, despite GnRH stimulation apparently adequate to induce ovulation, gonadotrophin levels were still low (LH 1·1 U/l, FSH 1·3 U/l, ratio 0·8:1), and no statistically significant pulses of LH could be identified. Following menstruation, despite continuing GnRH treatment, oestrogen creatinine ratios fell to below 10 μg oestrogen/g creatinine and remained suppressed for a further 70 d despite an increase in the dose of GnRH to 0·3 μg/kg. During this period of desensitization mean basal levels of LH varied from 0·4 to 4·1 U/l and FSH from 1·7 to 4·0 U/l. Changes in neither basal gonadotrophin levels, LH:FSH ratio (varying from 0·2:1 to 1·2:1), nor pulse frequency appeared to have any effect on ovarian activity. Ultrasound scans continued to demonstrate the presence of multiple small follicles (4–13 mm diameter). After 28 d of treatment with 0·3 μg/kg/90 min, GnRH treatment was discontinued and the patient subsequently conceived on hMG.

The pattern of LH secretion in response to GnRH administration in one women with hyperprolactinaemic amenorrhoea is shown in Fig. 2. Two serial sampling periods were carried out before treatment was started, one preceding, and one following a week of treatment with 0·9% saline solution, 40 μl/90 min s.c. given via the same infusion pump. On each occasion LH:FSH ratio was less than one and only one pulse of statistically

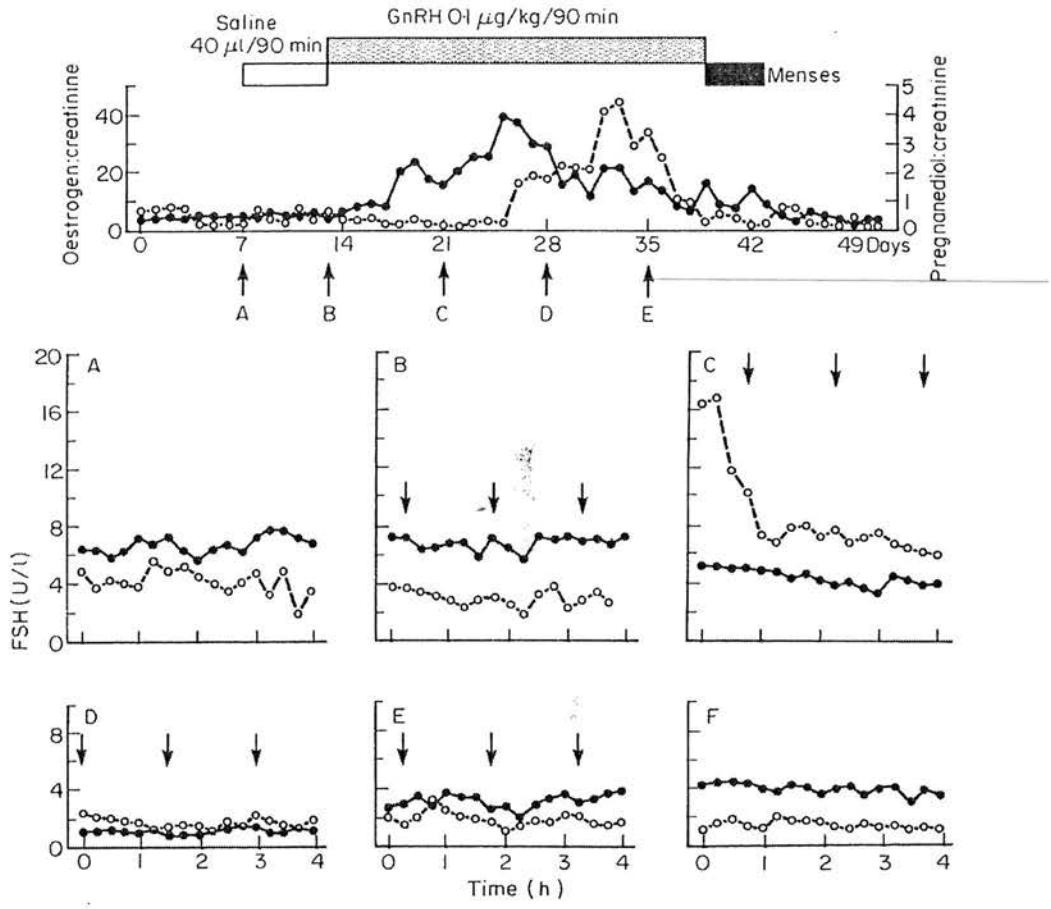


Fig. 2. Daily oestrogen:creatinine (●——●) and pregnanediol:creatinine (O- - -O) ratios during GnRH administration to one woman with idiopathic hyperprolactinaemia (basal PRL 2281 mU/l): 0·1 μg/kg/90 min GnRH resulted in ovulation and menstruation. The pattern of LH (O- - -O) and FSH (●——●) secretion before (A + B) and at various time points during the course of treatment (CD + E) are shown below. A final serial sampling episode (F) was carried out 2 months after cessation of treatment when the patients was once again amenorrhoeic (↓ denotes a pulse of saline at B or GnRH at C, D, E).

significant LH secretion could be identified. The LH:FSH ratio was reversed during the mid-follicular phase of the cycle, although on this occasion no significant pulse of LH secretion was identified and no temporal relationship between exogenous GnRH pulses and endogenous LH could be determined. Both LH and FSH concentrations were suppressed during the early and late luteal phases. Thus, despite successful induction of an apparently normal ovulatory cycle we were unable to demonstrate that this had been achieved by the restoration of a normal physiological pattern of LH secretion. A further serial sampling episode was carried out 62 d after cessation of GnRH administration when LH:FSH ratio was seen to have fallen to 0·4:1. Two statistically significant pulses of LH secretion could be identified, but basal LH concentration was low (1·3 U/l ± 0·1 SEM).

Table 3. Mean concentrations of LH and FSH, LH:FSH ratio, number of pulses/4 h and mean pulse amplitude together with follicle number in relation to days of treatment with various doses of GnRH for patient A in group A

| Dose | Day | LH (U/l) | FSH (U/l) | LH:FSH | Pulses/4 h | Mean pulse amp (U/l) | Number of follicles | E:C ratio | P:C ratio |
|---|---|---|---|---|---|---|---|---|---|
| Pretreatment | | 1·3 | 1·9 | 0·7:1 | 0 | | None | 2·6 | 0·2 |
| 0·1 μg/kg/90 min | | 1·5 | 2·9 | 0·5:1 | 1 | 1·7 | None | 3·1 | 0·1 |
| | 7 | 2·1 | 4·4 | 0·5:1 | 1 | 3·5 | 5 | 19·6 | 0·14 |
| | 14 | 3·1 | 2·7 | 1·1:1 | 2 | 1·6 | 2 | 9·3 | 0·11 |
| | 21 | 4·1 | 3·4 | 1·2:1 | 2 | 2·2 | 1 | 4·4 | 0·22 |
| | 28 | 3·0 | 2·6 | 1·2:1 | 1 | 1·8 | 2 | 4·2 | 0·06 |
| | 35 | 2·0 | 2·5 | 0·8:1 | 0 | — | 5 | 2·4 | 0·13 |
| | 42 | 1·7 | 2·4 | 0·7:1 | 1 | 1·5 | 3 | 3·4 | 0·15 |
| 0·2 μg/kg/90 min | 8 | 1·1 | 1·3 | 0·8:1 | 0 | — | 2 | 26·1 | 0·1 |
| | 15 | 1·4 | 1·5 | 0·9:1 | 1 | 0·6 | 2 | 4·2 | 1·15 |
| | 21 | 2·0 | 2·0 | 1·1 | 2 | 1·0 | None | 7·9 | 1·01 |
| | 28 | 2·5 | 4·0 | 0·6:1 | 1 | 1·1 | 2 | 3·3 | 0·2 |
| | 35 | 0·9 | 2·0 | 0·5:1 | 1 | 1·1 | 1 | 4·0 | 0·2 |
| | 42 | 0·4 | 2·0 | 0·2:1 | 0 | — | 1 | 3·0 | 0·1 |
| | 56 | 4·1 | 5·7 | 0·7:1 | 2 | 3·5 | 4 | 2·3 | 0·3 |
| | 70 | 3·9 | 4·0 | 1:1 | 1 | 1·7 | 3 | 8·5 | 0·3 |
| 0·3 μg/kg/90 min | 7 | 3·5 | 3·5 | 1:1 | 2 | 2·6 | 6 | 4·4 | 0·3 |
| | 14 | 3·6 | 3·5 | 1:1 | 1 | 2·7 | 4 | 3·3 | 0·2 |
| | 21 | 3·1 | 2·6 | 1·2:1 | 1 | 1·8 | 3 | 5·1 | 0·2 |
| | 28 | 0·7 | 1·7 | 0·4:1 | 2 | 1·4 | None | 6·3 | 0·4 |

E:C, Oestrogen:creatinine (μg/g).
P:C, Pregnanediol:creatinine.

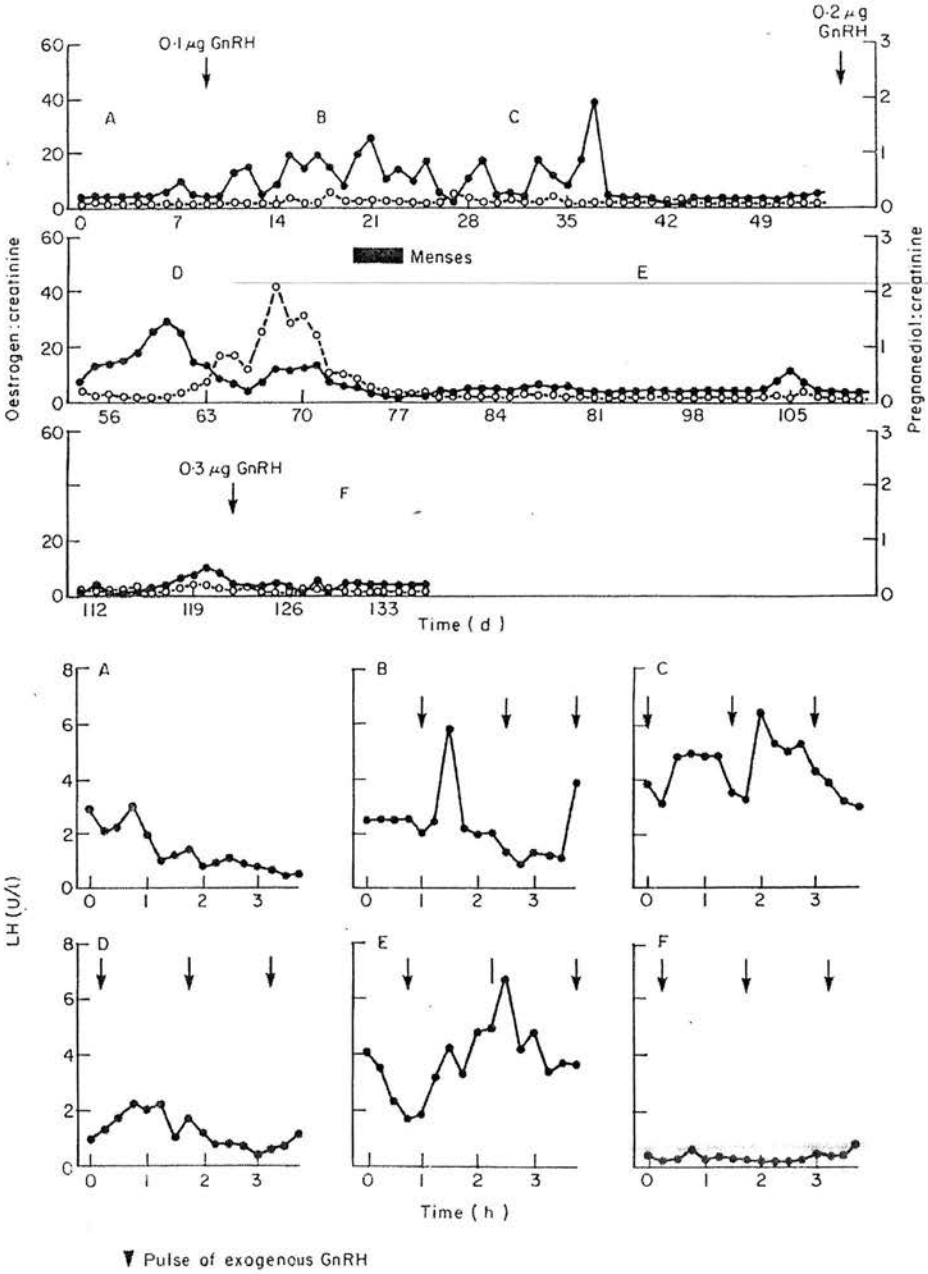


Fig. 3. Daily oestrogen:creatinine (●——●) and pregnanediol:creatinine (O– – –O) ratios during GnRH administration to one woman in group A, hypogonadotrophic hypogonadism (patient A): 0·1 μg/kg GnRH administered from day 9 resulted in follicular development only followed from day 38 by desensitization. Increasing the dose of GnRH to 0·2 μg/kg resulted in ovulation and menstruation followed by desensitization despite increasing the dose by another increment. The pulsatile pattern of secretion of LH (●——●) at various time points during the course of treatment (A–F) are shown below. ↓ denotes a pulse of exogenous GnRH from the pump.

The pattern of ovarian activity demonstrated in the patient from group B in whom desensitization followed ovulation is shown in Fig. 1. During the period of densitization mean basal LH during serial sampling episodes varied from 4·3 U/l ± 0·7 SEM to 13·6 U/l ± 3·0 SEM. No consistent pulsatile pattern of secretion of LH could be identified. Immediately following disconnection of the pump from the site of administration of GnRH (anterior abdominal wall) a 5-$\mu$g dose of GnRH was given s.c. into the upper arm, this resulted in a 300% increase in LH concentration within 20 min of administration.

## DISCUSSION

Ovulation was successfully induced with s.c. administered pulsatile GnRH in 6/8 women with hypogonadotrophic amenorrhoea; in 3/6 women with an elevated LH:FSH ratio; and in 2/2 women with idiopathic hyperprolactinaemia. Although theoretically, successful ovulation induction with pulsatile GnRH, at least in women with hypogonadotrophic hypogonadism, should result from the establishment of a pattern of LH secretion consistent with that seen in a normal cycle, we were unable to demonstrate this. Moreover, we were unable to demonstrate a constant relationship between either the pattern of LH secretion or the LH:FSH ratio with the prevailing pattern of ovarian activity.

Desensitization was observed in 5/14 women and to our knowledge this phenomenon has not previously been reported in association with the pulsatile administration of GnRH. Results from the episodes of serial sampling carried out during periods of desensitization suggest that while at times pituitary secretion of LH became refractory to GnRH stimulation, at other times both the pattern of LH secretion and the LH:FSH ratio appeared to be sufficient to induce at least follicular development, suggesting refractoriness at an ovarian level. Desensitization may have arisen as a result of an inadequate dose or pulse frequency of GnRH or as a result of the route of administration. While we used a dose of GnRH smaller than that administered in many treatment programmes (Mason *et al.*, 1984; Abdulwahid *et al.*, 1985), ovulation was successfully induced in a proportion of women sufficient to suggest that desensitization was not the result of inadequate amounts of GnRH. Furthermore, desensitization is more likely to occur with excessive GnRH (Knobil, 1980; Wildt *et al.*, 1981) than with too little. While it has been suggested that GnRH pulse frequency is important for the induction of normal ovarian activity (Knobil, 1980) most treatment regimes use at least a 90-min pulse interval. Moreover, there is some evidence to suggest that, at least in women with hypogonadotrophic hypogonadism, the pituitary-ovarian axis may respond adequately to pulse frequencies which fall within a tolerable range rather than to one critical frequency (Wildt *et al.*, 1981; Crowley *et al.*, 1985; Santoro *et al.*, 1986). Desensitization therefore seems most likely to have resulted from the route of administration. Pharmacokinetic differences in s.c. and i.v. routes of GnRH administration have been described (Reid *et al.*, 1981; Handelsman *et al.*, 1984; Menon *et al.*, 1984). Administered s.c., GnRH absorption is prolonged and delayed, and peak values significantly reduced. Chronic administration of any substance s.c. may lead to problems at the injection site. Menon *et al.* (1984), using a heparinized preparation of GnRH given s.c., reported the frequent development of haematomas at the site of injection. Skarin *et al.* (1982) reported pituitary unresponsiveness in a hypogonadal male patient treated with heparinized GnRH, treatment was successful when heparin was removed from the preparation. While

we did not use heparin to administer GnRH by the route and while the site of injection was changed frequently (and seldom did we observe signs of infection at the site), a local subclinical inflammatory response may interfere with GnRH absorption. The dampening of both plasma GnRH and LH profiles known to occur may in effect convert a pulsatile pattern of administration into a continuous infusion pattern of GnRH. Both pituitary and gonadal desensitization have been observed in monkeys (Knobil, 1980) rats (de Koning *et al.*, 1979) and in humans (Rabin & McNeil, 1980) with GnRH given as a continuous infusion.

Desensitization was not demonstrated in either of the women with idiopathic hyperprolactinemia but treatment was discontinued after one ovulatory cycle since both patients had previously responded satisfactorily to oral bromocriptine therapy.

In conclusion, we have found a variable response to s.c. pulsatile GnRH therapy in women with anovulation of different origins and suggest that, perhaps because of the route of administration, both pituitary and gonadal desensitization may occur. Nonetheless, because of the potential hazards of out-patient i.v. therapy, including venous thromboembolism and sepsis, we believe that GnRH should be given initially to all patients by the s.c. route.

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# The World Health Organization Multinational Study of Breast-feeding and Lactational Amenorrhea. I. Description of infant feeding patterns and of the return of menses

*World Health Organization Task Force on Methods for the Natural Regulation of Fertility*

*United Nations Development Programme/United Nations Population Fund/World Health Organization/World Bank Special Programme of Research, Development and Research Training in Human Reproduction, World Health Organization, Geneva, Switzerland*

**Objective:** To detect differences between populations in both infant feeding practices and the duration of lactational amenorrhea, if they exist.

**Design:** Prospective, nonexperimental, longitudinal follow-up study.

**Setting:** Five developing and two developed countries.

**Patient(s):** Four thousand one hundred eighteen breast-feeding mothers and their infants.

**Intervention(s):** Breast-feeding women collected ongoing information about infant feeding and family planning practices, plus the return of menses. Fortnightly follow-up occurred in the women's homes.

**Main Outcome Measure(s):** Breast-feeding frequency by day (and by night); 24-hour breast-feeding duration, percent of all infant feedings that were milk/milk-based (and solid/semisolid foods); time until the end of full breast-feeding; time until regular supplementation; and time until the end of lactational amenorrhea.

**Result(s):** Differences between the centers in the duration of amenorrhea were substantial, ranging from a median of 4 months in New Delhi (India) to 9 months in Chengdu (China). Women in developed countries (but also women in Chengdu) were more likely to delay supplementation (for up to 5 months), whereas women in Santiago (Chile), Guatemala City (Guatemala), and Saganu (Nigeria) started supplements much earlier, sometimes as early as 1 week after birth.

**Conclusion(s):** Both breast-feeding behavior and the duration of lactational amenorrhea vary markedly across settings, indicating that breast-feeding promotion and family planning advice should be site- and culture-specific. (Fertil Steril® 1998;70:448–60. ©1998 by American Society for Reproductive Medicine.)

**Key Words:** Breast-feeding, lactation, amenorrhea, infant feeding, fertility, postpartum, international

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Breast-feeding suppresses the resumption of ovarian activity after childbirth and thus is associated with a period of infertility (1, 2). The duration of infertility varies between individual women, between societies, and appears to depend largely on infant feeding practices. Several studies have suggested that full unsupplemented breast-feeding protects against pregnancy (3–5), and some investigators even have argued that the contraceptive effect of breast-feeding can be relied on as long as the total daily duration of suckling exceeds a certain threshold (6). However, in at least two countries, Chile (7) and Mexico (8), full unsupplemented breast-feeding does not always appear to be associated with inhibition of ovulation, and some fully breast-feeding mothers do conceive. The apparent differences observed between populations may be an artifact related to differences in study design and in definitions of the key variables.

The return of menses during breast-feeding may be the most important readily observable correlate of returning fertility. The first menses is a definitive sign of the need for contraception for women who do not want to become pregnant (9–11). Although the return of menses is an imperfect reflection of the recovery of postpartum fertility, it virtually always is a sign of some kind of ovarian activity.

We report the findings of a large, prospective, longitudinal, multinational study designed to detect differences between populations in breast-feeding practices and the duration of lactational amenorrhea. We describe the infant feeding practices observed in seven different cultures and the duration of amenorrhea in these settings. A companion article explores the relation between feeding practices (and other variables) and the duration of amenorrhea (12), and future reports will address pregnancy, postpartum bleeding patterns, infant growth in relation to breast-feeding practices, and center-specific results.

## MATERIALS AND METHODS

### Subjects

Seven centers were chosen to participate in the study. Five centers were in developing countries. These centers were located in Chengdu (China), Guatemala City (Guatemala), New Delhi (India), Sagamu (Nigeria), and Santiago (Chile). Two centers were in developed countries. These centers were located in Uppsala (Sweden) and in two sites in Australia (Melbourne and Sydney, each of which contributed half the required number of subjects.)

In Chengdu, women in rural townships were recruited by a government research institute. In Guatemala City, women were recruited through a government maternity hospital. In the Melbourne/Sydney center, women were recruited by a private periurban hospital outside of Sydney and by the medical research institute of an academic hospital in periurban Melbourne. In New Delhi, women were recruited by a government research institute involved in maternal and child health in south Delhi. In Sagamu, women were recruited through a government teaching hospital. In Santiago, women who had their infants at a large urban university hospital were recruited. Finally, in Uppsala, women were recruited in the university hospital after delivery.

Based on existing data and allowing for a discontinuation rate of 10%, it was calculated that 528 mother-infant pairs would need to be recruited in each center to detect a between-center difference of 1 month in the median duration of lactational amenorrhea. Each center initially was asked to recruit 550 women, and the target was changed according to the discontinuation rate.

Women had to be aged between 20 and 37 years and to have had no more than three previous live births. To minimize the number of dropouts from the study, women were required to have breast-fed one infant for at least 4 months. Women also had to be literate, intent on breast-feeding their baby for at least 6 months, and of "normal nutritional status" (i.e., neither obviously malnourished nor obese). Their infants had to be singletons, vaginally delivered at term (≥37 weeks), and above the 10th percentile in birth weight (or ≥2.5 kg if norms for the population were unavailable). Both mother and infant were required to be healthy when they were entered into the study.

Mothers who intended to use hormonal contraception or to have interval sterilization that would involve separation from the infant for more than 8 hours and those who had a history of spontaneous irregular menstrual cycles (<21 or >35 days) were not recruited, and neither were mothers who were suckling more than one child or infants who were being breast-fed by more than one mother. If this situation arose during the study, the mother-infant pair was withdrawn.

This study was approved by the World Health Organization Secretariat Committee on Research Involving Human Subjects. Local ethical committee approval also was obtained in all centers, and all mothers participating in the study gave informed consent.

### Methods

Mothers were admitted to the study within 7 days of delivery. At admission, personal histories and the socioeconomic status of both the mother and her partner as well as medical and obstetric histories of the mother were recorded. Details of the pregnancy, delivery, and postpartum period, and of the mother's diet and use of nutritional supplements and measures taken to prepare for breast-feeding also were documented.

The mother's height, weight, and upper arm circumference and the infant's weight, length, and head circumference were recorded in all centers at admission to the study and then at monthly intervals. The skinfold thickness of the mother and the chest circumference of the infant also were measured monthly in all but one of the centers. Standard scales, tape measures, and calipers were provided to all centers. The mother's body mass index (BMI) was calculated as her weight (in kilograms) at 6–8 weeks postpartum per her height (in meters) squared.

Mothers were instructed to fill in a card on which they recorded the daily number of breast-feeding episodes and manual breast expressions, the number and type of any supplementary feeds, and vaginal bleeding and spotting (separately). Any episodes of illness of either the mother or the infant, together with any medications used, also were recorded. For 24 hours every 2 weeks, a detailed record day chart was completed in which the timing and duration of each breast-feeding episode were recorded. The type and amount of supplementary food and when (in relation to a breast-feed) and how (via cup, spoon, or bottle) it was given also were noted.

Only suckling episodes that lasted at least 2 minutes and were separated by 30 minutes or more were recorded as breast-feeds. Episodes that occurred within the same 30-minute period were recorded as a single breast-feed. The same time limits were applied to the definition of an episode of manual expression. Breast-feeds that started after 10 PM but before 6 AM were defined as night feeds.

Any substance the infant received that was not maternal milk sucked from the breast was defined as a supplement. Supplements were divided into four categories: water or noncaloric fluids; caloric fluid feeds; milk or milk-based feeds, including expressed breast milk; and semisolid or solid feeds. If more than one type of supplement was given, the episode was classified according to a hierarchy in which solids were regarded as more important than milk-based supplements, which were more important than caloric fluids, which were more important than water and noncaloric fluids. A supplement was considered as a "taste" if less than the equivalent of 2 teaspoons (10 mL) was given.

For the purposes of the present analysis, three breast-feeding categories were defined: full breast-feeding when the infant received only breast milk, vitamins, medicine, and/or other noncaloric fluids, or tastes of the other categories of supplements; partial breast-feeding when the infant received caloric supplements in amounts greater than tastes; and weaned when the infant no longer was being breast-fed.

The commencement of regular supplementation was defined as the point at which at least seven supplementary feeds were given for the first time in each of two successive 2 week periods, with the starting time taken as the midpoint of the earlier 2-week period. In the variable TRS (time to regular supplements) (A), all food and fluids are regarded as supplements so the infant is receiving only breast milk. In TRS(B), water and noncaloric fluids are not regarded as supplements, and in TRS(C), only milk or milk-based feeds and solids or semisolids are regarded as supplements so that, for example, fruit juice or sweet tea is not counted as a supplement.

Follow-up visits were made every 2 weeks in the mother's home. At each follow-up visit, the breast-feeding card and the detailed record day chart were checked and the data were transferred to a standard follow-up form. The first detailed record day chart was completed during the third week of the infant's life, with a follow-up visit arranged for the next day. At each follow-up visit, mothers were asked whether the detailed record day was a typical day, and, whenever possible, they were asked to avoid days that often might be atypical (e.g., weekends) and to ensure a 14-day interval between recordings of detailed infant feeding patterns.

Whenever possible, follow-up visits were made by the same person and arrangements were made to visit at exactly 2-week intervals. Visiting workers were asked to avoid as much as possible giving mothers advice that might interfere with spontaneous infant feeding behavior unless it was obvious that the mother, the infant, or both were failing to thrive. At each follow-up visit, the mother was asked whether she believed that she was pregnant. If so, arrangements were made to confirm the pregnancy by clinical examination, pregnancy test, and/or ultrasound scan.

Mothers were withdrawn from the study when pregnancy was confirmed or when they had experienced two normal menstrual periods. Subjects were free to withdraw from the study at any time for any other reason. An additional form was completed when the infant was weaned. Completed forms were checked by the principal investigator and sent regularly to the Special Programme of Research, Development and Research Training in Human Reproduction at the World Health Organization in Geneva, Switzerland.

Infant feeding patterns were analyzed for all subjects who continued to breast-feed and remained amenorrheic. When a subject weaned her infant or when menses resumed (confirmed as a first menses by the occurrence of a second menstrual bleed or pregnancy), she was excluded from further analysis. The discussion that follows relates to data analyzed in this way with values taken from the detailed record day charts.

Women who weaned their infants before a first menses were included in a separate analysis of breast-feeding frequency until they left the study. In this case, breast-feeding frequency and duration per 24 hours were set to zero (rather than the subject being excluded). When weaned infants were included, the breast-feeding trends and the relative positions of the centers were unchanged, but the absolute values of the infant feeding variables tended to be slightly lower.

Menses was defined as 2 consecutive days of vaginal bleeding with at least 1 day requiring sanitary protection. Any bleeding that occurred within 14 days of the end of lochia was ignored, as was bleeding associated with a gynecologic procedure such as the insertion of an intrauterine device (13). To use menses as an indication of fertility, it was decided to ignore bleeding episodes that were unlikely to be followed by ovulation. Thus, for a bleeding episode to be defined as a first menses, it had to be followed by a second episode (of at least 2 days' duration with at least 1 day requiring sanitary protection) that occurred >21 days but <70 days later. (In all centers, only 0.8% of first bleeding episodes were followed by a second episode within 21 days; however, 20.7% were followed by a second episode after an interval of >70 days.)

A bleeding episode that was not followed by a second episode within 21–70 days was ignored and the next episode then was defined as the first menses. Only one bleeding episode could be ignored in this way. Thus, a first menses can be described as "confirmed" by a second episode within the time limits or "unconfirmed" if the subject left the study for some reason before having a second bleeding episode.

Conception can occur only if ovulation occurs, and thus a pregnancy conceived during amenorrhea was treated as if it were a confirmed first menses, with the date of menstruation (and thus the end of amenorrhea) imputed as the date of conception plus 15 days. If a woman conceived after a vaginal bleeding episode and if the date of conception plus 15 days (i.e., when menstruation would have occurred if the woman had not conceived) fell >21 days but <70 days after

TABLE 1

Study admissions and outcomes, by center.

| Admissions and outcomes | Center | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| | Chengdu | Guatemala City | Melbourne/ Sydney | New Delhi | Sagamu | Santiago | Uppsala | Total |
| Total no. of admissions | 541 | 688 | 624 | 550 | 520 | 690 | 505 | 4,118 |
| No. of women with two menses | 460 | 519 | 466 | 456 | 415 | 564 | 457 | 3,337 |
| No. of pregnancies | 29 | 17 | 14 | 9 | 5 | 3 | 8 | 85 |
| No. who withdrew from the study | 52 | 152 | 144 | 85 | 100 | 123 | 40 | 696 |

the first bleeding episode, then the pregnancy served to designate the first bleeding episode as a confirmed first menses. If the date of conception plus 15 days fell <21 days or >70 days after the first vaginal bleeding episode, then the date of conception plus 15 days was taken as the date of the confirmed first menses and the first vaginal bleeding episode was disregarded.

Application of these rules to the data of the 3,337 subjects who reported two menstrual periods each, the 85 subjects who became pregnant, and the 150 subjects who left the study after the first reported menses yielded 3,264 episodes of confirmed and 307 unconfirmed first menses.

When a vaginal bleeding episode occurred, women were asked whether the blood loss was greater than, less than, or equal to that experienced during a normal menstrual period. The first episode that she believed was equal to or greater than a normal menstruation was defined as the first menses according to the woman's perception.

Thus, for the purpose of the study, the end of amenorrhea could be defined in three ways: [1] by the onset of a vaginal bleeding episode >14 days after the end of lochia that was not associated with a gynecologic procedure, lasted at least 2 days, and required sanitary protection for at least 1 day (the first reported bleeding); [2] by a menstrual bleed confirmed as the first menses by the onset of a second episode meeting the criteria described earlier ("the HRP rule," an algorithm created by the Human Reproduction Programme of the World Health Organization for this study); and [3] by the woman's perception of a first menses.

### Statistical Analyses

Data collected at the time of recruitment to the study, such as maternal parity and infant birth weight (admission characteristics), were summarized as means for quantitative variables and as percentages for categorical ones. Differences between centers were tested with the use of analysis of variance and the associated $F$ tests and $\chi^2$ tests.

Time until the end of full and partial breast-feeding status was calculated with the use of survival analysis, and for each breast-feeding status, the 50th percentile of the distribution was taken as the summary index. Observed times for those who had their first menses or withdrew from the study before the end of each breast-feeding status were censored. The distribution of time to the start of regular supplementation also was calculated with the use of survival analysis. Survival times of subjects who withdrew from the study for any reason as well as those who had their first menses before they had started providing their infants with regular supplementation were censored.

The distribution of the duration of lactational amenorrhea was calculated with the use of a survival analysis, with the 50th percentile of the distribution taken as the summary index. Observed survival times of subjects who withdrew from the study before the end of amenorrhea were censored. Center estimates were compared with the use of either the log rank test or Wilcoxon's test. Survival analysis was done with the use of PROC LIFETEST of the software package Statistical Analysis Systems (SAS), version 6.8 (SAS Institute, Cary, NC).

## RESULTS

Of the 4,118 women recruited for the study, 3,422 reached one of the two end points of the study: 3,337 had two normal menstrual periods and 85 became pregnant. A total of 696 women withdrew for various reasons; 150 of these withdrawals took place after the occurrence of the first menses. Table 1 shows the number of women admitted to the study at each center and the number who completed and withdrew from the study.

There were three main reasons for withdrawal: the subject wanted to withdraw (213 women, ranging from 13 in Uppsala to 70 in Melbourne/Sydney); the subject was lost to follow-up (208 women, ranging from 3 in Uppsala to 51 in Santiago); and the subject began using a hormonal method of contraception (107 women, ranging from none in New Delhi

TABLE 2

Selected admission characteristics of mothers and infants, by center.

| Characteristic | Center | | | | | | |
|---|---|---|---|---|---|---|---|
| | Chengdu | Guatemala City | Melbourne/ Sydney | New Delhi | Sagamu | Santiago | Uppsala |
| Mean no. of previous live births | 1.0 | 1.7 | 1.6 | 1.5 | 1.9 | 1.5 | 1.4 |
| Mean no. of infants previously breast-fed | 1.0 | 1.7 | 1.5 | 1.4 | 1.9 | 1.5 | 1.4 |
| Median duration (mo) of breast-feeding (last child) | 16 | 13 | 12 | 18 | 10 | 12 | 8 |
| Median duration (mo) of full breast-feeding (last child) | 7 | 1 | 5 | 5 | 1 | 4 | 5 |
| Median duration (mo) of amenorrhea (last child) | 8 | 4 | 8 | 2 | 6 | 3 | 7 |
| Mean (±SE) time (h) from delivery to first breast-feed | 39.7 ± 0.9 | 7.5 ± 0.2 | 1.4 ± 0.3 | 6.8 ± 0.3 | 10.5 ± 0.3 | 8.0 ± 0.2 | 0.6 ± 0.1 |
| Percentage of infants breast-fed within 1 hour | 0 | 1 | 58 | 0 | 0 | 0 | 76 |
| Percentage of infants given food/fluid before first breast-feed | 97 | 19 | 3 | 35 | 84 | 99 | 1 |
| Mean (±SE) birth weight (kg) | 3.3 ± 0.02 | 3.2 ± 0.02 | 3.6 ± 0.02 | 3.0 ± 0.02 | 3.2 ± 0.02 | 3.4 ± 0.02 | 3.8 ± 0.02 |
| Mean (±SE) length at birth (cm) | 49.1 ± 0.09 | 49.9 ± 0.07 | 51.6 ± 0.09 | 49.7 ± 0.09 | 50.2 ± 0.11 | 50.8 ± 0.07 | 51.8 ± 0.08 |
| Mean (±SE) mother's BMI ($kg/m^2$) at 6 weeks postpartum | 21.5 ± 0.08 | 24.8 ± 0.12 | 24.8 ± 0.14 | 21.4 ± 0.13 | 24.5 ± 0.12 | 24.8 ± 0.06 | 24.0 ± 0.12 |

*Note:* The numbers from which the means and percentages were calculated for each characteristic are approximately the same for each center as the total number of admissions in Table 1, except for the mean duration of amenorrhea after the last child, for which numbers for the seven centers, respectively, are 533, 618, 517, 497, 652, 451, and 564.

to 32 in Melbourne/Sydney). Most women were still breast-feeding at the time that menses returned.

The mean age of the mothers varied from 26.2 years in New Delhi to 30.9 years in Melbourne/Sydney. In each center, except the Australian center, the study sample consisted of one predominant ethnic group. Almost all the subjects were married and came from urban areas, with the exception of New Delhi and Chengdu, where 20% and 99%, respectively came from rural areas. The mothers had completed the least number of years of education in Chengdu (mean, 5.3 years) and the most in Melbourne/Sydney (mean, 14.3 years).

The protocol dictated that every subject had breast-fed at least one child of her own. The mean number of live births varied from 1.0 in Chengdu to 1.9 in Sagamu. Previous breast-feeding experience is shown in Table 2. Whereas the reported median total duration of breast-feeding of the last child was shortest in Uppsala (8 months), the median duration of full breast-feeding was shortest in Guatemala City and Sagamu (1 month) and associated amenorrhea was shortest in New Delhi (2 months), where women had breast-fed their last child for the longest period (>18 months). In all centers except New Delhi and Santiago, the median duration of amenorrhea extended beyond the median duration of full breast-feeding of the last child.

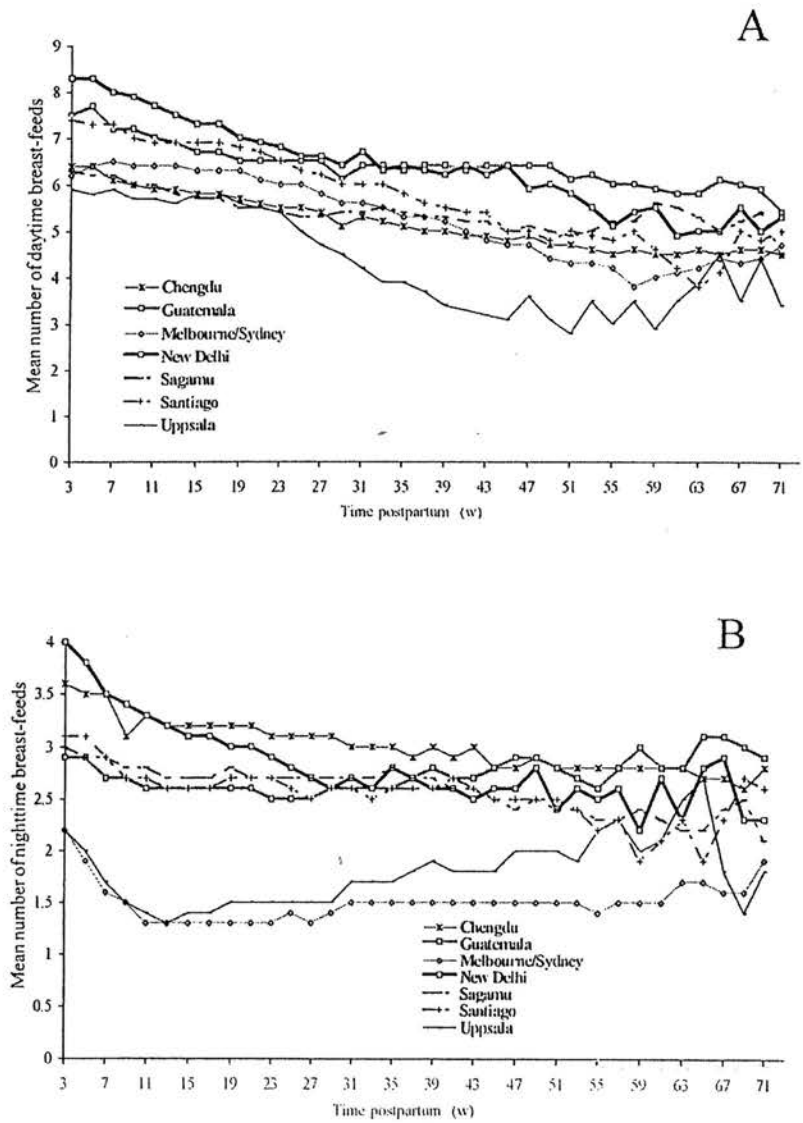
More than 90% of the infants were delivered in a hospital or health center, except in Chengdu, where 73% of the infants were delivered at home. The interval between delivery and the first breast-feeding episode varied significantly between centers ($P < .001$) (Table 2). In Melbourne/Sydney and Uppsala, the infant usually was put to the breast within 2 hours of delivery before any other food or fluids were given. In contrast, almost all the infants in Chengdu and Santiago were given some food or fluid before the first breast-feed, which did not occur for a mean of almost 40 hours after delivery in Chengdu.

Infant weights and anthropometric measurements varied significantly ($P < .001$) between centers (Table 2), with the smallest infants born in New Delhi (mean admission weight, 3.0 kg) and the largest in Uppsala (mean admission weight, 3.8 kg). Statistically significant differences in BMI were observed among the mothers ($P < .001$) (Table 2).

Less than 3% of the women in each center were vegetarian, except in New Delhi, where 77% were vegetarian. Only in Santiago did a substantial proportion (21%) of women smoke during pregnancy, only 7% smoked in Uppsala and fewer elsewhere. Alcohol consumption during pregnancy was highest in Melbourne/Sydney (64%) and Uppsala (59%) and lowest in Guatemala City (6%) and New Delhi, where no mother drank alcohol during pregnancy.

FIGURE 1

Mean number of breast-feeds, by time and by center. (A), Daytime breast-feeds. (B), Nighttime breast-feeds.



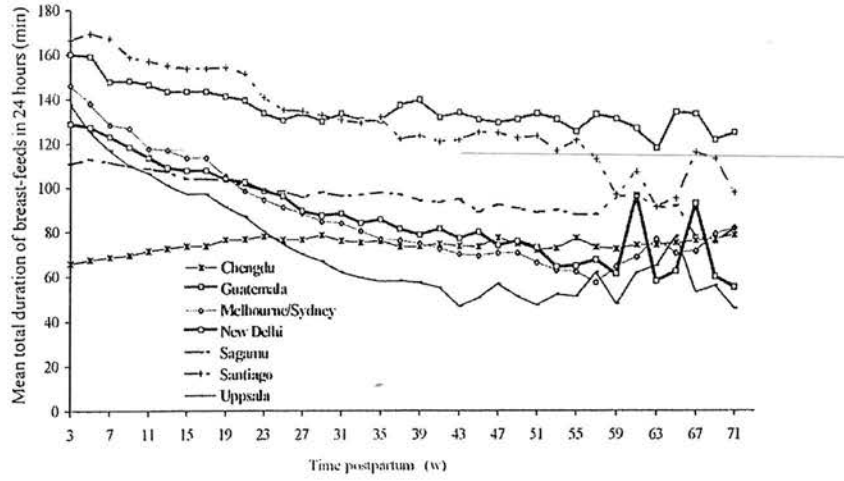

## Infant Feeding Patterns During Lactational Amenorrhea

Differences in infant feeding patterns between centers can be seen when daytime (6 AM to 10 PM) and nighttime (10 PM to 6 AM) feeds are considered separately (Fig. 1). Breast-feeding at night occurred least often in the two developed country centers (Melbourne/Sydney and Uppsala) and was most common in Chengdu and New Delhi. In Chengdu, infants were breast-fed three times at night for the first year of their lives.

In all centers except Chengdu, the mean number of breast-feeding episodes and the mean total duration of breast-feeding each day fell with time after birth (Fig. 2). This fall

FIGURE 2

Mean total duration of breast-feeding per 24 hours among all women who remained amenorrheic, by time and by center.




was most noticeable in Uppsala. In Chengdu, whereas the number of breast-feeding episodes fell with time after birth, the mean total duration of breast-feeding per 24 hours increased gradually over the first 6 months and thereafter remained fairly constant throughout. Nevertheless, for the first 4–6 months of life, infants in Chengdu spent the least amount of time breast-feeding. Infants in Uppsala spent twice as long breast-feeding each day compared with infants in Chengdu, and infants in Santiago spent nearly three times as long breast-feeding each day compared with infants in Chengdu.

In all centers, as the frequency of breast-feeding declined with time after birth, the longest interval during which the mother was not exposed to the suckling stimulus increased. Mothers in Chengdu and New Delhi consistently experienced the shortest interval between breast-feeds. In both centers, the infant was almost 1 year old before the longest interval between breast-feeds lasted more than 6 hours. In contrast, the average infant in Guatemala City, Melbourne/Sydney, and Uppsala was going more than 6 hours without breast-feeding by 6 weeks of age.

There were marked differences between centers in patterns of supplementation. In Chengdu, Melbourne/Sydney, and Uppsala, breast milk accounted for >90% of the infant's intake for the first 18 weeks after birth. In Uppsala, however, once supplementation was started, it progressed rapidly. In contrast, in Chengdu, 70% of the infant's feeds still included breast milk at 1 year after birth.

Mothers in New Delhi and Sagamu were much more likely to give their infants water or noncaloric fluids in the early weeks—and indeed throughout the study—than were mothers in the other centers, where water and noncaloric fluids were introduced only gradually. Mothers in Guatemala City and Santiago were more likely to give their infants caloric fluids than in the other centers and, at approximately 22 weeks postpartum, ≥5% of the infant's feeds consisted of caloric fluids compared with <2.5% in all other centers.

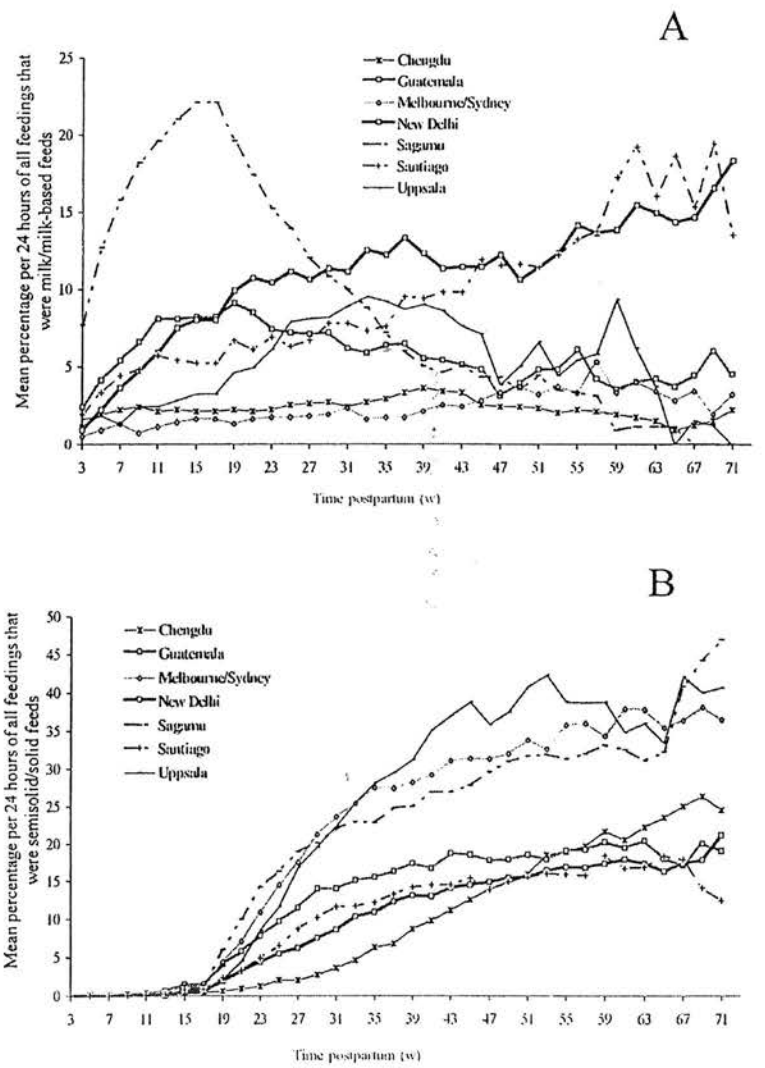
Caloric fluids did not account for >10% of the number of feeds (and in most cases, ≤5%) in any center, even when the infant was more than 1 year old. Up to approximately 20 weeks of age, milk or milk-based feeds (Fig. 3A) were most likely to account for a substantial number of feeding episodes in Sagamu, whereas at 14 weeks of age, >20% of the infant's feeds were of this nature. In this center, milk or milk-based feeds declined in frequency after about 16 weeks, when solid or semisolid feeds (Fig. 3B) were introduced.

In all other centers except New Delhi and Santiago, milk or milk-based feeds accounted for ≤10% of the infant's feeds, and in Chengdu and Melbourne/Sydney, this type of supplement seldom was important. In New Delhi and Santiago, supplementation with milk or milk-based feeds increased gradually with time throughout the study, accounting for approximately 12% of feeds at 1 year of age. In all centers, the percentage of total feeds that consisted of solid or semisolid foods rose markedly from 16 weeks after birth, but the rate of introduction was slowest in Chengdu.

All centers showed a decline in the prevalence of full breast-feeding over time, but the pattern varied among the

FIGURE 3

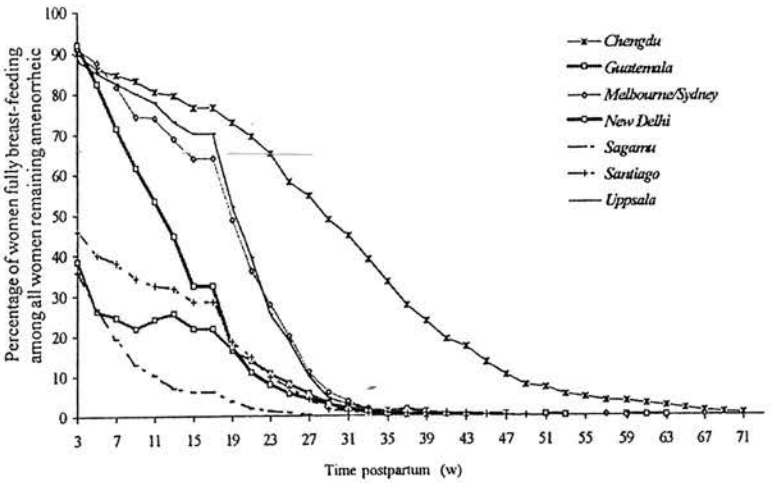
Mean percentage of all feeds in 24 hours that are milk or milk-based feeds and solid or semisolid feeds among all women who remained amenorrheic, by time and by center. (A), Milk or milk-based feeds. (B), Semisolid or solid feeds.




centers (Fig. 4). In all centers except Chengdu, full breast-feeding had virtually ended by 30 weeks. In contrast, in Chengdu, 55% of mothers were still breast-feeding fully at approximately 6 months postpartum. The median and mean times until the end of each of the breast-feeding categories for the women who experienced amenorrhea is shown in Table 3. Women in Melbourne/Sydney and Uppsala fully breast-fed for a median of approximately 3.5 months. In Guatemala City, Sagamu and Santiago, less than one-half of the mothers ever fully breast-fed.

FIGURE 4

Percentage of women fully breast-feeding among all women who remained amenorrheic, by time and by center.




## Start of Regular Supplementation

The time to the start of regular supplementation is shown in Table 4. In Melbourne/Sydney and Uppsala, there is little difference among the three categories of supplements, which suggests that when supplementation starts, it does so with caloric food. Regular supplementation with water and non-caloric fluids starts in Chengdu at a median of 153 days (21–22 weeks) and caloric supplements of any description are delayed until approximately 34 weeks after birth. In contrast, women in Sagamu start giving regular caloric feeds (milk or milk-based or solid or semisolid) from a median of 4 weeks after birth.

## Return of Menses

The concordance among the three definitions of the end of amenorrhea in each center is shown in Table 5. The concordance was highest in Chengdu, where in 92% of cases the woman's perception of a first menses matched that defined as a first menses by the HRP rule, which in 94% of cases also was the first reported bleed. In 96% of cases in Chengdu, the first reported bleed was the same as or heavier than a normal menstrual period. In Uppsala, in 90% of cases the first reported bleeding episode subsequently was confirmed to be the first menses (and thus the end of amenorrhea); however, in only 68% of cases was the first bleeding episode believed

TABLE 3

Time (median and mean no. of days) from delivery to the end of full and partial breast-feeding, by center.

| | Amount of breast-feeding | | | |
|---|---|---|---|---|
| | Full | | Partial | |
| Center | Median | Mean (95% CI) | Median | Mean (95% CI) |
| Chengdu | 192 | 150 (141–159) | 557 | 279 (266–291) |
| Guatemala City | 7 | 25 (22–27) | 581 | 182 (172–192) |
| Melbourne/Sydney | 107 | 99 (94–103) | 490 | 234 (223–245) |
| New Delhi | 78 | 68 (64–72) | 495 | 142 (132–151) |
| Sagamu | 7 | 21 (18–23) | 396 | 213 (203–224) |
| Santiago | 7 | 34 (31–38) | 493 | 163 (154–171) |
| Uppsala | 111 | 98 (93–103) | 295 | 208 (199–217) |

*Note*: CI = confidence interval.

TABLE 4

Time (median and mean no. of days) until the start of regular supplementation, by center.

| | Time to regular supplementation (TRS) | | | | | |
|---|---|---|---|---|---|---|
| | TRS(A)* | | TRS(B)† | | TRS(C)‡ | |
| Center | Median | Mean (95% CI) | Median | Mean (95% CI) | Median | Mean (95% CI) |
| Chengdu | 153 | 132 (124–140) | 237 | 177 (168–186) | 265 | 200 (191–209) |
| Guatemala City | 24 | 54 (49–58) | 26 | 57 (52–61) | 122 | 100 (95–105) |
| Melbourne/Sydney | 161 | 142 (137–146) | 162 | 145 (141–150) | 164 | 147 (142–151) |
| New Delhi | 51 | 53 (50–56) | 94 | 86 (82–91) | 95 | 89 (84–93) |
| Sagamu | 12 | 12 (12–12) | 14 | 32 (29–35) | 26 | 40 (37–43) |
| Santiago | 27 | 55 (51–59) | 67 | 72 (67–76) | 148 | 114 (109–119) |
| Uppsala | 152 | 139 (134–144) | 152 | 141 (137–146) | 153 | 142 (137–147) |

*Note*: Regular supplementation occurred when at least seven supplementary feeds were given for the first time in each of two successive 2-week periods. CI = confidence interval.

* TRS(A): Time to regular supplementation where a supplement is water, a noncaloric fluid, a milk or milk-based supplement, or a solid or semisolid food.

† TRS(B): Same as TSR(A) except that water and noncaloric fluids are not considered to be supplements.

‡ TRS(C): Same as TRS(B) except that caloric fluids also are not considered to be supplements.

by the women to be the same as or heavier than a normal period. Combining all centers, 89% of the first bleeding episodes were confirmed by a second and 80% of these first bleeding episodes matched the woman's perception of a first menses.

## Duration of Lactational Amenorrhea

The median duration of lactational amenorrhea in each center, calculated with the use of each of the definitions of a first menses, is shown in Table 6. In this table, estimates from all confirmed and all first menses are shown. In all centers, the median duration of amenorrhea was shortest when defined by the onset of the first vaginal bleeding episode, which preceded the woman's perception by as little as 5 days in Chengdu and as much as 44 days in Santiago. In all centers except Melbourne/Sydney and Uppsala, lactational amenorrhea was longest when defined by a confirmed first menses according to the HRP rule; in the two developed country centers, it was longest when defined by the woman's perception. The difference between the duration defined by a confirmed first menses and that defined by the woman's perception varied from 1 day in Melbourne/Sydney to 23 days in Sagamu.

There were statistically highly significant differences between centers in the median duration of lactational amenorrhea. Chengdu's value is significantly higher than all the others. Melbourne/Sydney's value also is significantly

TABLE 5

Concordance among the three rules for the definition of the end of amenorrhea: number (percentage) of women whose values on both variables were the same, by center.

| Center | Woman's perception same as HRP rule* No. (%) | Woman's perception same as first reported bleed† No. (%) | HRP rule same as first reported bleed No. (%) |
|---|---|---|---|
| Chengdu | 497 (91.9) | 521 (96.3) | 508 (93.9) |
| Guatemala City | 516 (75.0) | 526 (76.5) | 594 (86.3) |
| Melbourne/Sydney | 484 (77.6) | 462 (74.0) | 576 (92.3) |
| New Delhi | 443 (80.6) | 477 (86.7) | 475 (86.4) |
| Sagamu | 463 (89.0) | 489 (94.0) | 476 (91.5) |
| Santiago | 496 (71.9) | 485 (70.3) | 573 (83.0) |
| Uppsala | 360 (71.3) | 341 (67.5) | 456 (90.3) |
| All centers | 3,259 (79.1) | 3,301 (80.2) | 3,658 (88.8) |

* HRP rule defines the end of amenorrhea as a menstrual bleed (at least 14 days after the end of lochia, not associated with a gynecologic procedure, lasting at least 2 days, and requiring sanitary protection for at least 1 day) confirmed as the first menses by the onset of a second episode.

† First reported bleed is a menstrual bleed at least 14 days after the end of lochia, not associated with a gynecologic procedure, lasting at least 2 days, and requiring sanitary protection for at least 1 day.

TABLE 6

Duration of lactational amenorrhea: time (median no. of days) from delivery to the end of amenorrhea, by amenorrhea definition and by center.

| | End of amenorrhea defined by | | | |
|---|---|---|---|---|
| | HRP rule* | | | |
| | Confirmed first menses* | All first menses† | Woman's perception | First reported bleeding episode‡ |
| Center | Median (95% CI) | Median (95% CI) | Median (95% CI) | Median (95% CI) |
| Chengdu | 282 (266–304) | 277 (261–300) | 273 (252–290) | 268 (250–282) |
| Guatemala City | 209 (196–228) | 189 (175–205) | 191 (174–208) | 152 (137–167) |
| Melbourne/Sydney | 272 (258–285) | 268 (250–276) | 273 (258–289) | 248 (235–268) |
| New Delhi | 122 (111–134) | 118 (108–130) | 103 (96–117) | 93 (86–99) |
| Sagamu | 234 (215–255) | 222 (205–237) | 211 (188–227) | 205 (180–223) |
| Santiago | 171 (156–183) | 159 (145–175) | 159 (147–175) | 115 (105–127) |
| Uppsala | 230 (221–241) | 224 (217–235) | 239 (227–251) | 214 (204–223) |

*Note*: CI = confidence interval.

* HRP rule defines the end of amenorrhea as a menstrual bleed (at least 14 days after the end of lochia, not associated with a gynecologic procedure, lasting at least 2 days, and requiring sanitary protection for at least 1 day) confirmed as the first menses by the onset of a second episode.

† Same as HRP confirmed first menses rule except that cases are included even if they dropped out of the study after the first menses but before the occurrence of the second, confirming, menses.

‡ First reported bleed is a menstrual bleed at least 14 days after the end of lochia, not associated with a gynecologic procedure, lasting at least 2 days, and requiring sanitary protection for at least 1 day.

higher than that of all the other centers except Sagamu, whereas Guatemala City, Sagamu, and Uppsala show no statistically significant differences among themselves. Santiago and New Delhi are significantly different from each other and from every other center. Whichever definition of a first menses is used, the rank order of centers, in terms of the duration of amenorrhea, is basically unchanged.

## DISCUSSION

In this study, menses was chosen as a proxy for the recovery of ovulation and thus for the return of fertility because it is a discrete event that is easily recognized and recalled. Moreover, the collection of biochemical data on ovarian function would have been impractical in a study of this size.

In calculating the duration of amenorrhea as a surrogate for the duration of infertility associated with breast-feeding, we chose to ignore bleeding episodes that, by virtue of either a short (<21 days) or long (>70 days) interval before the occurrence of a second bleeding episode or pregnancy, seemed unlikely to have been either preceded or followed by ovulation.

In their detailed study of the return of fertility among 40 breast-feeding women in Manila, Eslami et al. (14) demonstrated that, for women who menstruated before 6 months postpartum, menses was a poor indicator of full fertility because only 25% of women who menstruated (defined as bleeding for ≥2 consecutive days) experienced ovulation within the next 30 days. Women who menstruated before 6 months experienced a mean interval of 8.4 weeks between the first menses and the first ovulation.

In the present study, when menses was defined using the HRP rule and only bleeding episodes confirmed to be a first menses were considered, between 21% (in Melbourne/Sydney) and 62% (in New Delhi) of women had their first menses before 6 months. If only 25% of these bleeds are likely to be associated with ovulation, then our estimation of the duration of infertility is shorter than it may have been in reality.

Other studies also have described a tendency for menses occurring in the first 6 months of lactation to be associated with anovulation. Campbell and Gray (15) compared women's descriptions of their bleeding episodes with their hormonal profiles in a study of the return of fertility in Baltimore. Ovulation occurred in only 35% of cycles in which bleeding was described as "light" or "spotting," whereas menses reported as "regular" or "heavy" (which would correspond to our definition of a woman's perception) were preceded by ovulation in 84% of cases.

It is clear that there are substantial differences between centers in the duration of lactational amenorrhea, with breast-feeding women experiencing a median of about 9 months of amenorrhea in Chengdu compared with about 3–4 months in New Delhi. There also are profound differences between centers in patterns of infant feeding: women in the developed country centers and in Chengdu were much more likely to delay the introduction of regular supplementary feeds until at least 3 months after birth (Table 3), whereas

women in Guatemala City, Sagamu, and Santiago started supplements when the infant was approximately 1 week old (Table 4). The factors influencing the duration of amenorrhea and any substantive differences among the centers are the subject of another article (12).

Some information about the infant feeding characteristics may seem contradictory when the centers are viewed relative to each other, but there are corresponding explanations, again in relative terms. For example, both a high breast-feeding frequency (Fig. 1) and the highest proportion fully breast-feeding (Fig. 4) are reported in Chengdu, yet this center reports the shortest duration of feeding in 24 hours (Fig. 2). This is because the average duration of suckling is short in Chengdu, the shortest of all seven centers. Similarly, Santiago reports the highest rate of milk or milk-based supplementation before 27 weeks of age (Fig. 3) and a low rate of fully breast-feeding (Fig. 4), yet the most minutes of breast-feeding in 24 hours in the first 27 weeks (Fig. 2). Mothers in Santiago reported long average suckling durations, the longest of all seven centers.

The subjects who were recruited to the study were chosen because they were highly likely to breast-feed successfully and therefore may not be representative of their communities, especially in terms of the duration of amenorrhea and the duration of the various types of breast-feeding (e.g., full, partial). In connection with this multicenter study, surveys of infant feeding patterns typical of the local area were undertaken in the developing country centers using the simplified methodology for community-based assessment of the duration of breast-feeding and amenorrhea (16). The durations of lactational amenorrhea in the simplified methodology surveys and in the current study (a woman's perception of a first menses) agreed within 1.8 months.

Although any differences may reflect selection bias due to our admission criteria, they also could be due to measurement effect: the surveys relied on recall, whereas our study measured the durations of breast-feeding and amenorrhea prospectively.

Although the infant feeding patterns of the subjects may not be representative of their country or region of residence, there was a difference of 1 month or less in each of five centers (not in Guatemala City and Santiago) between the mean of the women's perceived end of amenorrhea reported in the study and that recalled to be associated with the previous pregnancy (Table 2). This suggests that participation in the study did not of itself significantly influence infant feeding patterns.

This study detected profound differences in breast-feeding and supplementation practices across seven cultures, and profound variations in the duration of amenorrhea regardless of how the return of menses was defined. A companion article examines the relation between the length of lactational amenorrhea and feeding and other variables, controlling for center effects.

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# The World Health Organization Multinational Study of Breast-feeding and Lactational Amenorrhea. II. Factors associated with the length of amenorrhea

*World Health Organization Task Force on Methods for the Natural Regulation of Fertility*

*United Nations Development Programme/United Nations Population Fund/World Health Organization/World Bank Special Programme of Research, Development and Research Training in Human Reproduction, World Health Organization, Geneva, Switzerland*

**Objective:** To determine the relation between infant feeding practices (and other factors) and the duration of postpartum amenorrhea, and to establish whether there are real differences in the duration of postpartum amenorrhea for similar breast-feeding practices in different populations.

**Design:** Prospective, nonexperimental, longitudinal follow-up study.

**Setting:** Five developing and two developed countries.

**Patient(s):** Four thousand one hundred eighteen breast-feeding mothers and their infants.

**Intervention(s):** Breast-feeding women collected ongoing information about infant feeding and family planning practices, plus the return of menses. Fortnightly follow-up occurred in the women's homes.

**Main Outcome Measure(s):** A multivariate analysis explored the association between the risk of menses return and 16 infant feeding variables and 11 other characteristics.

**Result(s):** Ten factors (in addition to center effects) were significantly related to the duration of amenorrhea. Seven of these were infant feeding characteristics and the remaining three were high parity, low body mass index, and a higher frequency of infant illness.

**Conclusion(s):** The breast-feeding stimulus is strongly linked to the duration of postpartum amenorrhea. Cross-cultural effects also are extremely important and may have caused the variations in feeding, the variation in amenorrhea, or both. (Fertil Steril® 1998;70:461–71. ©1998 by American Society for Reproductive Medicine.)

**Key Words:** Breast-feeding, lactation, amenorrhea, infant feeding, fertility, postpartum, international

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Although the precise mechanisms underlying the inhibition of normal ovarian activity by breast-feeding are incompletely understood, there is general consensus that the duration of postpartum amenorrhea is strongly influenced by the pattern of infant feeding (1). Most investigators agree that the duration of breast-feeding is an important determinant of the length of amenorrhea, but there is less consensus about the role played by more precise measures of suckling activity.

The frequency of breast-feeds and their duration (2, 3), the maintenance of breast-feeding during the night (4, 5), and the introduction of food other than breast milk (2, 6) all have been shown in a number of studies to be critical factors in determining the duration of amenorrhea. Other investigators, however, have failed to confirm the importance of some of these variables (6–8).

Variables other than the many facets of infant feeding patterns that have been shown—or are thought—to influence the duration of lactation also may affect, perhaps independently, the duration of amenorrhea. These include the place of delivery (hospital or home) and the mother's employment (9); maternal age, parity, and education level (10); the use of pacifiers (11); the interval between delivery and the first breast-feed (12), and maternal nutritional status (13). Although it is difficult to imagine precisely how, it may be possible that subtle phys-

iologic differences between populations—and between individual women—themselves may account for some of the differences in the duration of amenorrhea reported from various countries by some investigators.

In a large multicenter study of different populations, we investigated the known and unknown factors that may influence the duration of amenorrhea in breast-feeding women. The purpose of this article is to determine the relation between infant feeding practices (and other factors) and the duration of postpartum amenorrhea, and to establish whether there are real differences in the duration of postpartum amenorrhea for similar breast-feeding practices in different populations.

## MATERIALS AND METHODS

A total of 4,118 breast-feeding mothers from seven centers (Chengdu, China; Guatemala City, Guatemala; Melbourne/Sydney, Australia; New Delhi, India; Sagamu, Nigeria; Santiago, Chile; and Uppsala, Sweden) kept a record of infant feeding from the first week postpartum until the second postpartum menses (n = 3,337), until pregnancy (n = 85), or until withdrawal from the study (n = 696), whichever came first. Mothers were aged 20–37 years, had previous breast-feeding experience, and were neither obviously malnourished nor obese. Their infants were all singleton, term, vaginal deliveries above the 10th percentile in birth weight (or ≥2.5 kg if norms for the population were unavailable).

Mothers kept a detailed record of infant feeding patterns, including the frequency, duration, and timing of breast-feeding episodes and the interval between them, and the frequency, type, and timing of supplementary feeds. They were visited at home every 2 weeks, at which time diary cards were checked and additional data on sexual activity, contraception, episodes of maternal and infant illness, and maternal diet were collected. The details of recruitment, admission characteristics of the subjects, and record-keeping are described in an accompanying article (14). This study was approved by the World Health Organization Secretariat Committee on Research Involving Human Subjects. Local ethical committee approval also was obtained in all centers and all mothers participating in the study gave informed consent.

Menses was defined as 2 consecutive days of vaginal bleeding with at least 1 day requiring sanitary protection. Bleeding that occurred within 14 days of the end of lochia or in association with a gynecologic procedure, such as intrauterine device insertion, was ignored. For a bleeding episode to be regarded as a confirmed first menses, it had to be followed by a second episode—meeting the same definitions—>21 but <70 days later, or by conception within 6–55 days (thus implying a second menses within the 21- to 70-day time limit). The end of amenorrhea thus was taken as the date of onset of the first menses. If conception occurred during amenorrhea, the end of amenorrhea was taken as occurring 15 days after the estimated day of conception. For a more detailed description of the basis for these definitions, see the accompanying article (14).

Application of these definitions to the data of the 4,118 subjects yielded 3,264 cases of confirmed first menses, 307 cases of unconfirmed first menses, and 547 remaining cases without a first menses.

The duration of amenorrhea was determined for each center by survival analysis in which the relevant event is the occurrence of a confirmed first menses and the dependent variable is thus the time from delivery to this occurrence. All other events, such as withdrawal from the study after an unconfirmed first menses or withdrawal from the study for any other reason, were censored (14). All seven centers first were compared in a group and then in pairs with the use of the log rank test or the Wilcoxon test, and the Bonferroni criterion was used to control the error rate in the multiple comparisons (15).

A total of 82 variables were evaluated regarding any possible relation with the duration of lactational amenorrhea. Of these, 31 were related to infant feeding and the remaining 51 covered admission characteristics of the mother and infant such as anthropometric measurements, including maternal body mass index (BMI, kg/m$^2$) at 6–8 weeks postpartum, maternal nutrition during pregnancy and follow-up, and maternal and infant illness. A number of variables were time-dependent and some, such as the time elapsed before 50% of feeds were supplements, were constructed specifically for the analysis. Each variable was analyzed initially by a univariate analysis using Cox's nonparametric hazards regression model (16).

Variables whose univariate test had a $P$ value of ≤.2 and those that, in the light of existing research in the area, were believed to be of biologic importance then were included in a multivariate regression analysis. Variables associated with previous pregnancies (e.g., the duration of breast-feeding of the previous child) were excluded. In this way, a total of 27 variables were selected for a final multivariate analysis also with the use of Cox's nonparametric hazards regression model (16). As used in the analysis, the hazard $h_i$ (t) of the return of menses at time t postpartum for the ith of N women in the study is postulated as follows:

$$h_i(t) = h_0(t) \exp\{\beta_1 x_{1i}(t) + \beta_2 x_{2i}(t) + \ldots + \beta_p x_{pi}(t)\}$$

where $x_{ji}(t)$ is the value at time t of the jth explanatory variable and the $\beta$s are regression coefficients.

Corresponding risk ratios are obtained by exponentiating the regression coefficients. Adjustment for any statistically significant differences between the centers was made by including a factor at seven levels for centers, with Chengdu as the reference. To examine differences between various

TABLE 1

Duration of lactational amenorrhea, by center.

| Center | Median duration (d) of lactational amenorrhea (95% CI) |
|---|---|
| Chengdu | 282 (266–304) |
| Guatemala City | 209 (196–228) |
| Melbourne/Sydney | 272 (258–285) |
| New Delhi | 122 (111–134) |
| Sagamu | 234 (215–255) |
| Santiago | 171 (156–183) |
| Uppsala | 230 (221–241) |

*Note:* CI = confidence interval.

pairs of centers, the analysis was repeated using each of the other centers as the reference, and the Bonferroni criterion was used to control the maximum experiment-wise error rate for these multiple comparisons (15). Modeling was done with the use of PROC PHREG of the software package Statistical Analysis Systems (SAS), version 6.8 (SAS Institute, Cary, NC).

Data on 4,091 of the 4,118 subjects were entered into the multivariate hazards model analysis. The remaining 27 subjects were excluded for missing at least 1 of the 27 variables. None of these 27 subjects had a confirmed first menses. Of the 4,091 subjects, 827 (20%) were censored, 520 for having no menses and the remaining 307 for having an unconfirmed first menses.

## RESULTS

The duration of amenorrhea varied from a median of 122 days in New Delhi to 282 days in Chengdu (Table 1). Unadjusted differences between the centers are highly significant ($P < .0001$). Chengdu's value is significantly higher than all the others. Melbourne/Sydney's value also is significantly higher than all the other centers except Sagamu, whereas Guatemala City, Sagamu, and Uppsala show no statistically significant differences among themselves. Santiago and New Delhi are significantly different from each other and from every other case.

Table 2 shows the estimated risk ratios and their 95% confidence intervals for the 27 variables included in the multivariate analysis. A risk ratio of >1.0 indicates a "risk" factor for the return of menses (i.e., an association with a shorter duration of amenorrhea). A risk ratio of <1.0 indicates a protective effect of the variable on the return of menses (i.e., an association with a longer duration of amenorrhea).

The risk of the return of menses was found to be significantly reduced by a higher number of live births, lower maternal BMI, higher proportion of visits at which the infant was reported to have been unwell, shorter interval between delivery and the first breast-feed, longer time to regular supplementation with any food or drink, longer total duration of breast-feeding in 24 hours, higher percentage of breast-feeds to total feeds, higher frequency of supplementation with water and noncaloric feeds, longer breast-feeding status as opposed to weaning, and longer duration between delivery and the time that supplements started to provide at least 50% of all feeds.

After adjustment for the 27 variables included in the multivariate analysis, estimates of the risk of the return of menses, and by inference the associated duration of amenorrhea, for the seven centers fall into three clusters. Chengdu, Melbourne/Sydney, and Sagamu, with the longest durations, show no statistically significant differences among themselves, whereas Melbourne/Sydney, Uppsala, and Guatemala City, which have the next-longest durations, show no statistically significant differences from each other; thus, Melbourne/Sydney straddles both groups. Santiago and New Delhi, with the shortest durations of lactational amenorrhea, are significantly different from each other and from the other two groups.

Thus, compared with the results of the unadjusted analysis, the main consequence of the adjustment is the elimination of the observed differences in the duration of lactational amenorrhea between Chengdu, Melbourne/Sydney, and Sagamu, as well as those between Melbourne/Sydney, Uppsala, and Guatemala City.

## DISCUSSION

There were statistically highly significant differences in the duration of amenorrhea among the centers (Table 1). These differences were reflected in the multivariate analysis as highly significant center differences (Table 2). In addition to the center differences, a total of 10 variables were significantly related to the duration of amenorrhea; 7 of these were related to the pattern of infant feeding and 3 were not.

### Infant Feeding Variables

Many of the breast-feeding variables are interrelated, and some provide only a slightly different way of defining the breast-feeding stimulus. It is not surprising, then, that only some of the infant feeding variables are significant in a multivariate analysis. For example, if most of the women breast-feed at night, then the "duration of nighttime breast-feeding" will be simply a subset of the variable "total duration of breast-feeding." Once the "total duration of breast-feeding" variable predicted a certain amount of amenorrhea duration, then the "nighttime duration of breast-feeding" variable was unable to predict any more.

Breast-feeding status (breast-feeding versus weaned) was found to be a highly significant variable, with the duration of amenorrhea strongly related to whether women were fully breast-feeding (i.e., breast-feeding in which the infant could receive water and other noncaloric fluids as supplements) or whether the infant had been weaned. Because the duration of

TABLE 2

Hazards model of the return of menses: risk ratios R and their 95% confidence intervals $R_L$ and $R_U$ for variables in the multivariate analysis.

| Variable | R | $R_L$ | $R_U$ |
|---|---|---|---|
| Non–infant feeding variables | | | |
| Years of education of mother | 0.997 | 0.985 | 1.009 |
| Number of live births | 0.894† | 0.845 | 0.946 |
| Infant's weight at admission | 0.924 | 0.845 | 1.011 |
| Sex of infant (M/F) | 1.062 | 0.989 | 1.140 |
| Maternal BMI at 6–8 weeks postpartum | 1.049† | 1.036 | 1.063 |
| Has the infant doubled its admission weight? (N/Y)* | 1.006 | 0.907 | 1.116 |
| Use of pacifier at around 1 month postpartum (N/Y) | 1.018 | 0.922 | 1.124 |
| Frequency of red meat consumption* | 1.005 | 0.988 | 1.021 |
| Percentage of visits when the infant had been unwell* | 0.997† | 0.995 | 0.998 |
| Was the mother working outside the home? (N/Y)* | 1.062 | 0.959 | 1.175 |
| Infant feeding variables | | | |
| Time interval between delivery and first breast-feed | 1.005‡ | 1.002 | 1.009 |
| Has regular supplementation with any food/drink started? (N/Y)* | 1.267§ | 1.056 | 1.520 |
| Has regular supplementation with caloric fluid or food started? (N/Y)* | 0.858 | 0.678 | 1.086 |
| Has regular supplementation with milk-based feeds or solids/semisolids started? (N/Y)* | 1.173 | 0.984 | 1.399 |
| Frequency of nighttime breast-feeding episodes* | 0.997 | 0.932 | 1.065 |
| Total frequency of breast-feeding in 24 hours* | 0.991 | 0.957 | 1.026 |
| Total duration of breast-feeding in 24 hours* | 0.997§ | 0.995 | 0.999 |
| Total duration of nighttime breast-feeding* | 1.003 | 0.998 | 1.007 |
| Average duration of suckling episode* | 1.005 | 0.992 | 1.017 |
| Percentage of feeds constituted by breast milk* | 0.991† | 0.988 | 0.995 |
| Frequency of water/noncaloric supplements* | 0.913† | 0.881 | 0.947 |
| Frequency of caloric fluid supplements* | 0.986 | 0.945 | 1.028 |
| Frequency of milk/milk-based supplements* | 1.010 | 0.985 | 1.036 |
| Frequency of solid/semisolid supplements* | 0.997 | 0.967 | 1.027 |
| Breast-feeding status | | | |
| Mainly breast-fed* | ref. | ref. | ref. |
| Partial breast-feeding* | 1.058 | 0.899 | 1.244 |
| Weaned* | 2.186† | 1.695 | 2.821 |
| Are supplements providing 50% of feeds? (N/Y)* | 1.203§ | 1.042 | 1.389 |
| Centers | | | |
| Chengdu | ref. | ref. | ref. |
| Guatemala City | 1.552† | 1.257 | 1.915 |
| Melbourne/Sydney | 1.305§ | 1.026 | 1.662 |
| New Delhi | 3.113† | 2.509 | 3.863 |
| Sagamu | 1.001 | 0.803 | 1.247 |
| Santiago | 2.233† | 1.818 | 2.742 |
| Uppsala | 1.580† | 1.234 | 2.023 |

*Note:* BMI = body mass index; F = female; M = male; N = no; ref. = reference ; Y = yes.

* Time-dependent variable.

† $P < .001$.

‡ $P < .01$.

§ $P < .05$.

lactational amenorrhea is related to the duration of breast-feeding, this observation is hardly surprising.

The total duration of breast-feeding per 24 hours also was a significant determinant of the duration of lactational amenorrhea. Few studies have measured the duration of suckling episodes. Howie et al. (2) demonstrated that the average duration of suckling each day was related more strongly to the resumption of fertility (for which first menses is the proxy in the current study) than the frequency of suckling episodes. Further, two studies that had a design similar to the study of Howie et al., one performed in Mexico (7) and the other in Egypt (8), were unable to show any relation between breast-feeding frequency and the return of ovulation.

Andersen and Schiøler (3), who studied a Danish population, and Stern et al. (17), who compared American women with !Kung hunter-gatherers, also described a positive relation between suckling duration and the length of amenorrhea or anovulation, as did Gray et al. (18). In the study by Gray et al., the relation was independent of suckling frequency (18).

Although it is thought that the suppression of fertility is related in some way to the disruption of the pulsatile release of GnRH from the hypothalamus (1), the mechanism by which the infant's suckling on the nipple might cause this disruption remains unclear. Whatever the mechanism, it seems logical to argue that the longer each day that the infant spends suckling, the more sustained will be the stimulus inhibiting ovarian activity and therefore the longer the duration of amenorrhea. It is possible that the amount of time that the infant spends suckling is a more direct or sensitive reflection of the stimulus that inhibits ovarian activity than the simpler measure of suckling frequency.

Some investigators (19) have found that the interval between suckling episodes also may influence the duration of amenorrhea. In this study, the longest interval between breast-feeds did appear to be a significant determinant of the duration of lactational amenorrhea in the univariate analysis ($P < .0001$); however, it was excluded from the multivariate analysis because a substantial proportion of values (16%) were found to be missing for this variable.

The other infant feeding variables that appear to have a significant influence on the duration of amenorrhea are related to supplementation. The later a woman started to give regular supplements (of any description), the longer she remained amenorrheic. The risk of a first menses increased substantially once 50% of the total number of feeds the infant received consisted of supplements (regardless of their nature) and the percentage of breast milk feeds declined.

Most investigators agree that the duration of amenorrhea is related to the pattern of supplementation (2, 18–21). Unfortunately, many neglect to define supplements, and it often is not clear whether water or caloric fluids (e.g., fruit juice) are regarded as such or not. Moreover, most make no distinction between tastes, occasional supplements, and regular supplementation.

Not all investigators agree, however, that supplementation has such a clear relation with the inhibition of fertility. Lewis et al. (6) found both the introduction of supplements and the amount given to the infant to be poor predictors of ovulation. In that study, water did not appear to have been classified as a supplement. In the study by Jackson et al. in Thailand (22), no correlation was found between the early introduction of supplements or the quantity consumed within the first 3 months postpartum and the duration of breast-feeding. However, in this study, water was not considered to be a supplement and it is not certain that variables associated with the duration of breast-feeding also are associated with the duration of lactational infertility.

In developed countries, supplements often replace a breast-feed, and this pattern was seen clearly among women in Uppsala, as described in the accompanying article (14). In developing countries, supplements are given more often in addition to breast milk, and in Guatemala City, Sagamu, and Santiago, the median time to first supplementation with caloric fluids or foods was only 7 days (14).

The influence of supplementation on suckling activity may depend on how it interacts with a breast-feed—even whether it is given before or after a suckling episode—as well as its caloric value. Supplements given after a breast-feed may have a negligible effect. Indeed, this is the basis of advice, albeit unproved, to breast-feeding women to suckle the infant first and give the supplement second. When supplementation significantly alters the percentage of time an infant spends suckling, it seems logical to argue that it reduces the stimulus to the inhibition of ovarian activity. An infant receiving nutritive supplements needs less breast milk to provide its daily caloric requirement. A less hungry infant may suck less often, for a shorter period, or perhaps less strongly.

Mothers who gave their infants water and noncaloric fluids to drink were more likely to experience a longer duration of amenorrhea. There were substantial differences between centers in the prevalence of supplementation with these fluids. In Uppsala, for example, water or noncaloric fluid accounted for <1% of the average infant's feeds for most of the first 6 months of age, whereas in Sagamu, water and unsweetened tea were given from the first week of life and accounted for at least 12% of the infant's feeds before 6 months of age (Fig. 1). Nevertheless, even after correcting for these center differences, supplementation with water or noncaloric fluids remained associated with longer durations of amenorrhea.

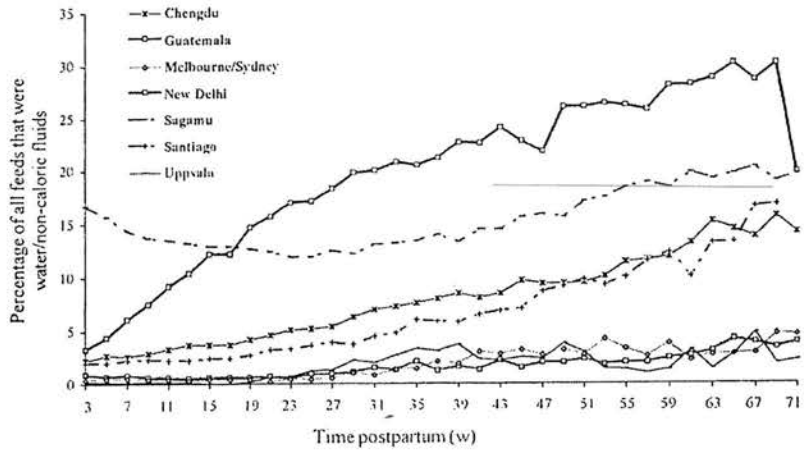
It seems unlikely that supplements that have no caloric value would somehow increase the amount of breast milk required by the infant. An analysis of the prevalence of supplementation with water showed that mothers who gave their infants more water or noncaloric fluids tended to breast-feed their infants more often. This trend was the same for nighttime (Fig. 2A) as well as for 24-hour breast-feeding episodes (Fig. 2B).

Further, mothers with a higher frequency of water and noncaloric fluid supplementation also tended to have the shortest interval between breast-feeds (Fig. 3). In view of the strong association between the longest interval between breast-feeds and the duration of lactational amenorrhea in the univariate analysis, exclusion of the former variable from the multivariate analysis because of sample loss problems might have increased the relevance of the prevalence of supplementation with water and noncaloric fluids as a correlate of the duration of lactational amenorrhea.

Mothers who gave supplements more frequently with water or noncaloric fluids also tended to give more milk or milk-based supplements (Fig. 4), although there was no obvious difference in the pattern of supplementation with solids or semisolids. During the first 6 months of life, some infants appeared to receive little supplementation with fluids of any sort and yet these were the infants who spent less time at the breast.

FIGURE 1

Percentage of all feeds that were water or noncaloric fluid, by time and by center.




The interval between delivery and the first breast-feed was a significant determinant of the duration of amenorrhea in that the early onset of suckling was associated with a longer duration of amenorrhea. Paradoxically, the center with the longest mean interval until the first breast-feed (40 hours after delivery) was Chengdu, which also was the center with the longest duration of amenorrhea. Nevertheless, in the multivariate analysis, the inverse relation was maintained after correcting for the effect of the individual centers.

A number of studies have reported a long duration of breast-feeding associated with the early onset of suckling; it is interesting that all were performed in developed countries. In a study in Dundee, Scotland, Salariya et al. (23) described a median duration of 182 days of breast-feeding among women who put their infant to the breast within 10 minutes of delivery compared with 77 days among women who delayed suckling for 4–6 hours. Similar results were obtained in the United States, Canada, and Norway (12). In contrast, a controlled, albeit small, study in Thailand was unable to show any deleterious effect on the duration of breast-feeding when the mother was separated from the infant in the immediate postpartum period for the purpose of sterilization (22).

It is possible that the effect may be more obvious in developed countries, where instrumental and operative deliveries and the use of narcotic analgesics are more common. However, one study in England (24) showed no effect of mode of delivery on the duration of breast-feeding. In the United Kingdom, women who are committed to breast-feeding are more likely to ensure that they suckle the infant as soon as possible after delivery. Many now incorporate this request into their "birth plan." In our study, only women who intended to breast-feed for at least 6 months were recruited; even so, it is possible that women who were more committed to breast-feeding tended to breast-feed sooner after delivery.

It is interesting to note that, in all centers except the two in developed countries, the median interval between delivery and the first breast-feed was >6.5 hours, and many infants (ranging from 19% in Guatemala City to 99% in Santiago) were given food or fluid before the first breast-feeding episode (14). This may change in the future as the result of "baby-friendly hospital" initiatives.

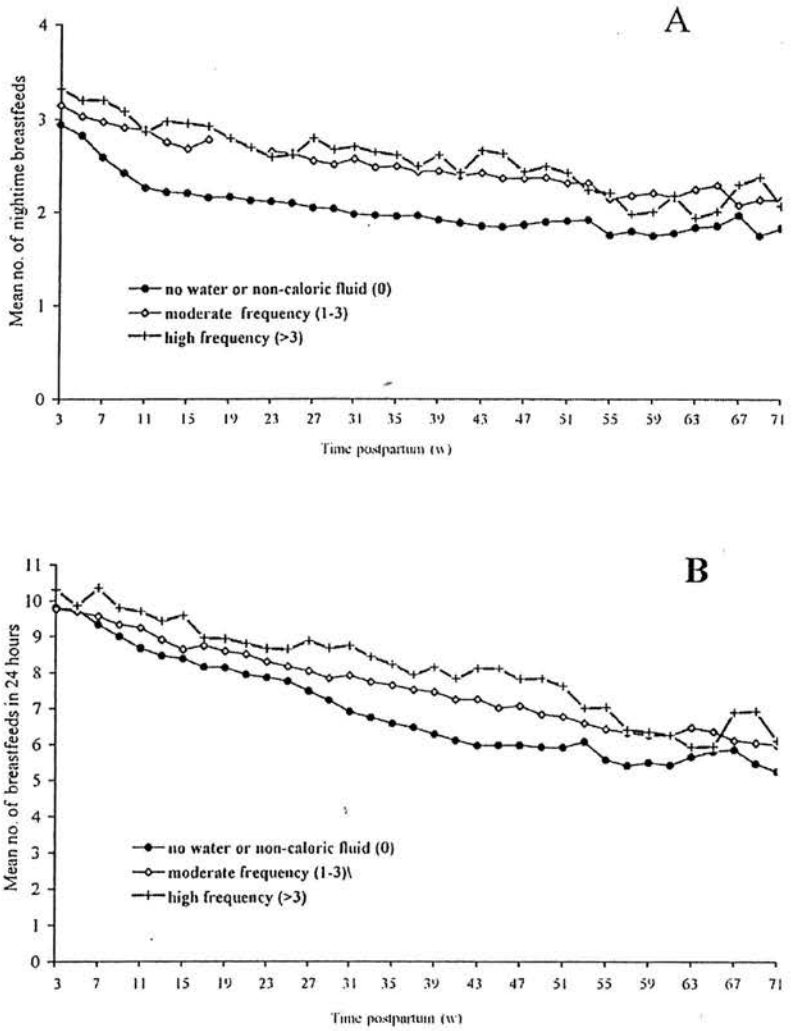
One result worthy of comment is the failure to find a significant association between the frequency of breast-feeds and the duration of amenorrhea. Some investigators (4, 5) have reported such an association. In our univariate analyses, the frequency of breast-feeding during the daytime, the nighttime, and over 24 hours each showed a highly significant relation with the duration of amenorrhea. However, in the presence of other variables in the multivariate analysis, they lost their importance. The validity of this finding is exemplified by the New Delhi center, which recorded the highest breast-feeding frequencies but the shortest duration of amenorrhea among the seven centers.

## Non–Infant Feeding Variables

Women who have had more previous live births may tend to experience longer durations of lactational amenorrhea. The influence of parity on the duration of breast-feeding has been recognized before, although, as with other variables, different investigators disagree about its effect. A review of World Fertility Survey data (25) from eight developing countries reported no consistent trends. In Bangladesh and

FIGURE 2

Mean number of breast-feeds, by time and by the frequency of water or noncaloric supplements, all centers combined. (A), Nighttime breast-feeds. (B), Total breast-feeds in 24 hours.



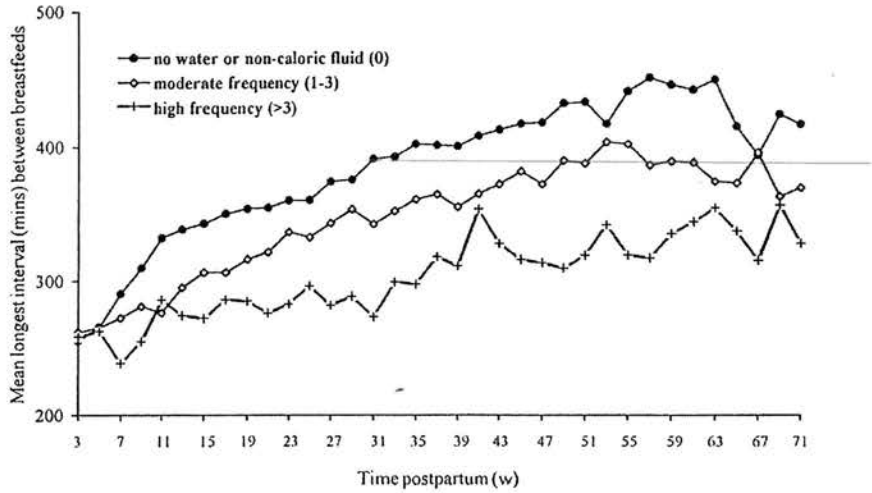

Indonesia, women of higher parity breast-fed their infants for shorter periods, whereas the opposite situation prevailed in Guyana, Panama, and Sri Lanka, where breast-feeding duration was longer among women with the most children.

Kurz et al. (26) described a positive effect up to parity three, but thereafter the relation disappeared among women in Guatemala City. Taylor et al. (12) found no correlation between parity and the duration of breast-feeding among American women. Higher parity may be associated with earlier supplementation, as in northern Thailand (22), where early supplementation was significantly associated with large household size. Family size may reflect socioeconomic status, which is known to have a negative effect on the duration of breast-feeding in developing countries (10).

The effect of parity on the duration of amenorrhea may be related to previous breast-feeding experience. In our study,

FIGURE 3

Mean duration of the longest interval between breast-feeds, by time and by the frequency of water or noncaloric supplements, all centers combined.




all participants had between one and three children and must have breastfed at least one of them. The experience and confidence gained from breast-feeding one child may increase the duration of breast-feeding of subsequent children.

At each follow-up visit, mothers were asked whether the infant had been ill and the nature of the illness and its duration were recorded. The percentage of visits at which the infant was reported to have been unwell correlated with the

FIGURE 4

Mean number of milk or milk-based supplements, by time and by the frequency of water or noncaloric supplements, all centers combined.

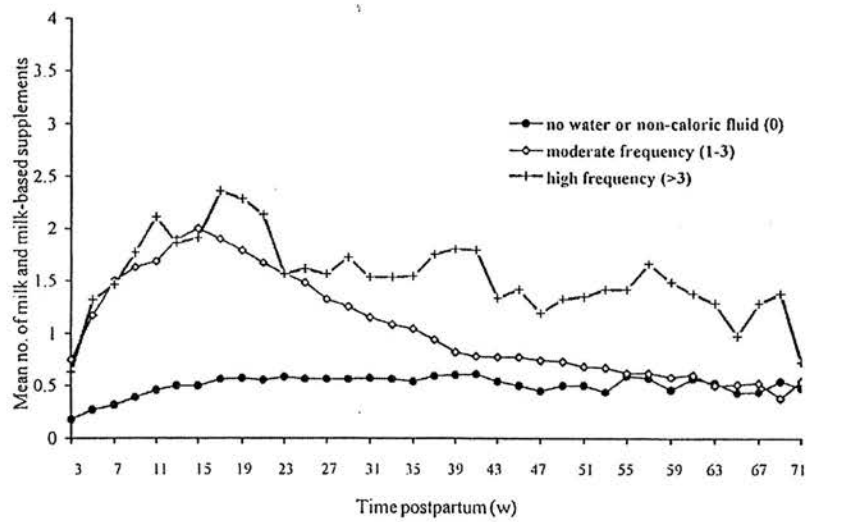
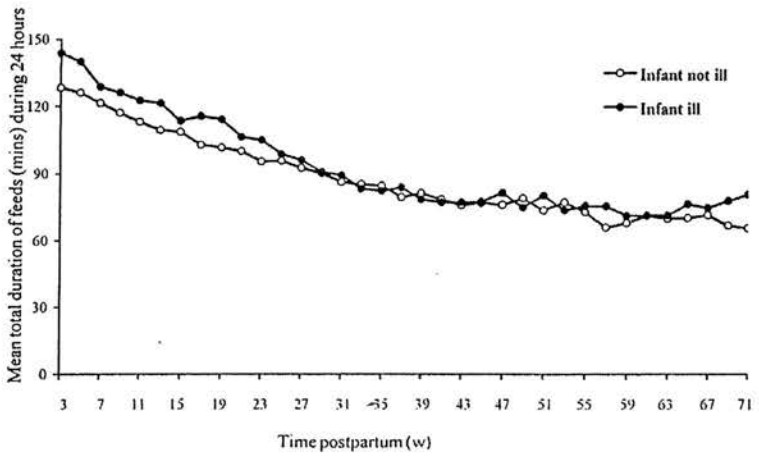


FIGURE 5

Mean total duration of breast-feeding in 24 hours, by time and by infant illness, all centers combined.




duration of amenorrhea, with more periods of illness leading to longer amenorrhea. To our knowledge, this relation has not been described before. In their study of women in northern Thailand, Jackson et al. (22) reported that infants with lower birth weights tended to receive supplemental feeds earlier. In the present study, low-birth-weight infants were not recruited and all infants had to be healthy at the time of entry into the study.

The number of infant deaths in each center was low: in all, only 14 infants died during the study, 5 of them in Chengdu and 3 in Sagamu, and even these deaths give substantially lower rates than the norms for China (41/1,000) and Nigeria (81/1,000) (27). Figure 5 suggests that when infants are unwell, the total duration of breast-feeds during 24 hours may be longer, up to the 22nd week postpartum. Perhaps mothers respond to an infant who is unwell by increasing the number of breast-feeds. Infants who were sick may have cried more often and been comforted by suckling.

Mothers with a lower BMI at the third follow-up visit (approximately 7 weeks after delivery) tended to have a longer duration of amenorrhea. The relation between maternal nutrition and the duration of amenorrhea has received substantial attention during the last 40 years (13). Because low body weight is known to be associated with pathologic amenorrhea (28), it seems reasonable to predict a relation between poor nutritional status and prolonged postpartum amenorrhea. Although some demographers have found little—or even no—effect (19, 20, 29), others have suggested that better maternal nutrition is associated with shorter amenorrhea (30). Even in those studies that indicate an effect of maternal nutritional status, the effect is small, with a difference of at most 6 weeks between malnourished and well-nourished mothers.

In the present study, obviously malnourished and obese women were excluded, and we have to assume that most mothers were well-nourished. A study of well-nourished breast-feeding women in Mexico (7) did report that women with a lower BMI were more likely to have prolonged amenorrhea, although overweight women were not excluded from participating in that study, and the range of BMI was from 17.0–33.8. Those investigators suggested that a higher percentage of body fat may be associated with an earlier return of menses. A strong, negative effect of BMI also was found by Popkin et al. (13).

A number of factors that have been shown in previous studies to affect the duration of lactational amenorrhea, including the sex of the infant, employment of the mother outside the home, and the use of pacifiers, were not found in the present multicenter study to have a significant effect. In the univariate analysis, both the duration of breast-feeding of the previous child and the duration of lactational amenorrhea in the past were found to be highly significantly related to the duration of amenorrhea experienced during breast-feeding of the index child ($P < .001$). In a second multivariate model that included the duration of amenorrhea with the previous child, the variable remained significant ($P < .001$) and the present results changed only slightly: the total number of previous live births lost its importance and the infant's weight at admission became significant.

Of profound importance is the effect of the center in which the study was undertaken. After the statistical adjust-

ment for 26 other factors in our analysis, there are still substantial differences in the duration of lactational amenorrhea between some centers and others, indicating that there may be other factors that influence the duration of amenorrhea that either were not recognized and measured or were measured inadequately in this study.

These other factors, we believe, show up in the significant center effects. The duration of amenorrhea in women in New Delhi, for example, was one-half that of women in Chengdu. In New Delhi, 77% of women were vegetarian, but in other centers almost everyone was nonvegetarian, so vegetarianism was not included as a variable in the multivariate analysis. The other dietary habits included were not found to be significantly related to the duration of amenorrhea. Although diet is known to affect patterns of menstruation (31), the effect of diet in our study was less pronounced than the total effect of the differences between centers.

In conclusion, 10 variables were identified that were associated with the duration of lactational amenorrhea. Some related to the way in which a woman feeds her infant, whereas others were a feature of the characteristics of the mother or infant. Some of the variables, such as breast-feeding status and parity, might have been anticipated on the basis of the results of previous studies and from our understanding of the physiology of lactational infertility. Others, such as the effect of water and noncaloric fluid supplementation, are more difficult to explain and may be mere associations, and not causal.

This is the largest known study of the effect of infant feeding patterns on the duration of amenorrhea. Some infant feeding variables undoubtedly are associated with, and probably influence, the duration of amenorrhea. In addition to these variables, however, there remain others that in this study appear as "center effects," which are associated with amenorrhea and probably with the duration of postpartum infertility.

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# The World Health Organization Multinational Study of Breast-feeding and Lactational Amenorrhea. III. Pregnancy during breast-feeding

*World Health Organization Task Force on Methods for the Natural Regulation of Fertility**

*United Nations Development Programme/United Nations Population Fund/World Health Organization/World Bank Special Programme of Research, Development and Research Training in Human Reproduction, World Health Organization, Geneva, Switzerland*

**Objective:** To determine the risk of pregnancy during lactational amenorrhea relative to infant feeding status.

**Design:** Prospective longitudinal study.

**Setting:** Five developing and two developed countries.

**Patient(s):** Four thousand one hundred eighteen breast-feeding mother-infant pairs.

**Intervention(s):** Infant feeding practices, menstrual status, and pregnancy were measured.

**Main Outcome Measure(s):** Life-table rates of pregnancy.

**Result(s):** In the first 6 months after childbirth, cumulative pregnancy rates during amenorrhea, depending on how the end of amenorrhea was defined, ranged from 0.9% (95% confidence interval [CI] = 0%–2%) to 1.2% (95% CI = 0%–2.4%) during full breast-feeding, and from 0.7% (95% CI = 0.1%–1.3%) to 0.8% (95% CI = 0.2%–1.4%) up to the end of partial breast-feeding. At 12 months, the rates ranged from 6.6% (95% CI = 1.9%–11.2%) to 7.4% (95% CI = 2.5%–12.3%) during full breast-feeding, and from 3.7% (95% CI = 1.9%–5.5%) to 5.2% (95% CI = 3.1%–7.4%) up to the end of partial breast-feeding.

**Conclusion(s):** These results support the Bellagio Consensus on the use of lactational amenorrhea for family planning, and confirm that the lactational amenorrhea method is a viable approach to postpartum contraception. (Fertil Steril® 1999;72:431–40. ©1999 by American Society for Reproductive Medicine.)

**Key Words:** Breast-feeding, lactation, infant feeding, amenorrhea, fertility, pregnancy, postpartum contraception, lactational amenorrhea method, LAM, international

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* See Appendix A.

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Breast-feeding is associated with the suppression of ovarian activity and thus with a variable period of amenorrhea and infertility (1). The risk of the resumption of fertility, and therefore of conception, during lactation is related to infant feeding patterns. Women who breast-feed their infants frequently and who delay the introduction of supplementary feedings tend to remain amenorrheic for a longer period (2, 3). A consensus meeting held in Bellagio, Italy in 1988 (4, 5) postulated that full or nearly full breast-feeding during lactational amenorrhea confers 98% protection against pregnancy in the first 6 months after childbirth. This degree of protection has been shown to be valid in several clinical studies (6–8). Although these clinical trials involved up to 485 women who were prospectively using the lactational amenorrhea method (LAM) (9) to avoid pregnancy, each study involved a homogeneous group of breast-feeding women, and one study (6) involved extraordinary support for breast-feeding. One multinational study concurred with these results but involved small numbers of women at each center (10).

A large prospective study was conducted to determine the relation between infant feeding practices and the duration of amenorrhea (11). This study also measured the occurrence of pregnancy among women in five developing and two developed countries. The purpose of this analysis was to determine the rate of pregnancy during lactational amenorrhea according

to infant feeding status among women in this multinational study to support or refute advice to breast-feeding women about the efficacy of lactational amenorrhea as a period of significant protection from pregnancy. This analysis has the following advantages: it includes a far larger number of women than has been studied similarly in the past, and no attempt was made to alter the indigenous infant feeding behaviors of the women who participated.

## MATERIALS AND METHODS

### Subjects and Procedures

Seven study centers participated in this research. They were located in Chengdu, China; Guatemala City, Guatemala; Melbourne/Sydney, Australia; New Delhi, India; Sagamu, Nigeria; Santiago, Chile; and Uppsala, Sweden. A total of 4,118 women were recruited into the study. The first participants were admitted in April 1989 and the last completed the study in December 1993. All were aged between 20 and 37 years at the time of entry into the study, had breast-feeding experience, and were literate. None was planning to use a hormonal method of contraception after childbirth, and all intended to breast-feed for at least 6 months. Women with a history of irregular menstrual cycles (<21 or >35 days) or of infertility were not recruited. The infants were all singletons who were delivered vaginally at term (≥37 weeks) and were above the 10th percentile in birth weight (or ≥2.5 kg if norms for the population were unavailable).

Mothers were admitted to the study within 7 days of childbirth. Each woman kept a daily record of the number of breast-feeding episodes and the number and type of any other foods or fluids (supplementary feedings) given to the infant. Days during which vaginal bleeding or spotting occurred also were recorded. For 24 hours every 2 weeks, a detailed record chart was completed in which the timing and duration of breast-feeding episodes were recorded, together with the details of supplementary feedings. Every 2 weeks, mothers were visited at home, where the feeding diaries were checked. At this visit, they were asked whether they had had intercourse since the previous visit and what method of contraception they were using (if any).

The return of fertility was the end point of the study. Because the detection of ovulation or measurement of hormone concentrations would have been impractical in a study of this size, the reappearance of regular cyclicity or the occurrence of pregnancy were regarded as proxies for the return of fertility. Thus, participation in the study continued until the woman experienced what she considered to be two normal menstrual periods or until conception occurred, whichever came first. At each follow-up visit, mothers were asked whether they thought they were pregnant. If the answer was "yes," arrangements were made to confirm the pregnancy, with a pregnancy test and/or an ultrasound examination.

Mothers who started using any hormonal method of contraception were discontinued from the study from the date of the introduction of such a method. The study protocol permitted the use of nonhormonal methods, but in the pregnancy analysis, the experience of users of such methods was restricted to the period before their introduction.

This study was approved by the World Health Organization Secretariat Committee on Research Involving Human Subjects. Local ethics committee approval also was obtained in all centers, and all women participating in the study gave informed consent.

### Definitions

#### *Bleeding Episode*

Bleeding per vaginam that lasted at least 2 days and required the use of sanitary protection for at least 1 day was defined as a menstrual bleeding episode. Bleeding episodes that occurred within 2 weeks of the end of lochia or that were associated with a gynecologic procedure, such as the insertion of an intrauterine device, were ignored.

#### *Confirmed First Menses—Human Reproduction Programme Rule*

A bleeding episode was confirmed as a first menses only if a second bleeding episode (meeting the same requirements listed earlier) occurred within the next 21–70 days. If a second episode occurred outside these time limits, the first episode was ignored and the second episode was defined as the first menses. Only one bleeding episode could be discounted. In this way, the first menses was "confirmed" by the "HRP rule" (named for the Human Reproduction Programme of the World Health Organization that created this algorithm for the study). A bleeding episode also could be confirmed as the first menses if conception occurred within the next 6–55 days, on the grounds that had conception not occurred, there would have been a second bleeding episode within 21–70 days. The main operational definition of the end of lactational amenorrhea in this study was the date of the confirmed first menses by the HRP rule.

During breast-feeding, a bleeding episode can occur as a consequence of ovarian follicular development followed by the withdrawal of estrogen (i.e., in the absence of ovulation). Bleeding also can follow ovulation with inadequate luteinization. Early "menstrual cycles" in breast-feeding women can be extremely irregular, indicating that ovarian activity is present but fecundity has not been restored. The HRP rule was created to more closely approximate the true return of fertility and not just the return of menses. By "confirming" that the first menses is part of a cyclic pattern, the HRP rule allows isolated bleeding episodes reflective of ovarian activity, but not true fertility, to be ignored.

#### *All First Menses—HRP Rule*

If the subject had one bleeding episode but discontinued participation in the study before the episode could be con-

firmed as a first menses by the HRP rule, this first "unconfirmed" menses was added to the confirmed first menses described earlier to comprise all first menses. Thus, this second operational definition of the end of lactational amenorrhea included all the cases of confirmed first menses but avoided the loss of cases in which a bleeding episode probably marked the return of fertility but the women were not observed long enough to confirm this. Undoubtedly, in some cases, this definition abbreviated the period of amenorrhea that would have been seen if the women had been followed up for a longer period.

### *All First Bleeding Episodes*

Because all bleeding episodes during the study were recorded, the end of amenorrhea also was defined as the date of the onset of the first bleeding episode, regardless of whether it qualified as a menses by the HRP rule. Thus, a third operational definition of the end of amenorrhea was studied, namely the first-ever bleeding episode. Although this definition included episodes of bleeding that clearly were not indicative of the return of fertility, this definition was included to compare the findings of this analysis with the results of other research. Other studies have defined the end of amenorrhea as the first bleeding episode without attempting to interpret the meaning of the bleeding in terms of the degree of fertility that it represents.

### *The Woman's Perception of the First Menses*

Finally, concerning each bleeding episode, the women were asked whether they perceived the bleeding to be more, less, or the same in amount as a normal menses. Thus, a fourth definition of the end of amenorrhea was explored, namely the first time that a woman perceived that the bleeding episode was a "normal" menses (i.e., that the amount of bleeding was the same or more than her former menses). This definition was called the woman's perception of the first menses.

### *Breast-feeding Status*

Breast-feeding status at the estimated time of conception in the women who became pregnant was defined in terms of three categories: full breast-feeding, in which the infant received only breast milk directly from the mother's breast and no other liquid or solids, or in which the infant received water and other noncaloric fluids or tastes of caloric supplements, vitamins, or medicine in addition to breast-feeding; partial breast-feeding, in which caloric supplements were given in amounts greater than tastes; and weaned, in which the infant was no longer being breastfed.

A more detailed description of the subjects, methods, and definitions used in this study was given in an earlier publication (11).

**TABLE 1**

Number of pregnancies during the study by breast-feeding status at the estimated time of conception, by contraceptive use at the estimated time of conception, and by study center.

| | Breast-feeding status at conception | | | | | | |
|---|---|---|---|---|---|---|---|
| | Full | | Partial | | Weaned | | |
| | Contraceptive use | | Contraceptive use | | Contraceptive use | | |
| Study center | No | Yes | No | Yes | No | Yes | Total |
| Chengdu | 13 | 2 | 7 | 2 | 2 | 3 | 29 |
| Guatemala City | — | — | 9 | 7 | 0 | 1 | 17 |
| Melbourne/Sydney | — | — | 5 | 4 | 3 | 2 | 14 |
| New Delhi | 1 | 0 | 4 | 2 | 2 | 0 | 9 |
| Sagamu | — | — | — | — | 3 | 2 | 5 |
| Santiago | — | — | 2 | 0 | 1 | 0 | 3 |
| Uppsala | — | — | 5 | 1 | 1 | 1 | 8 |
| All centers | 14 | 2 | 32 | 16 | 12 | 9 | 85 |

*Note:* Numbers represent the number of pregnancies.

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## Statistical Analyses

The median time until the start of intercourse and the use of contraceptives was calculated using survival analysis (12).

Survival analysis also was used to calculate cumulative pregnancy rates and their SEs during amenorrhea and up to the end of full and partial breast-feeding, with adjustment for the occurrence of sexual intercourse (i.e., including only those periods when intercourse was reported). The observed times for a subject were censored when she reached the end of amenorrhea; when she reached the end of each breast-feeding category; when she started using a method of contraception (coitus interruptus was included as a method), assuming that women were continuously protected by their method; and when she withdrew from the study. The rates were compared by $\chi^2$ test.

## RESULTS

In all, 3,422 women completed the study with a recognized fertility outcome: 3,337 were regarded as having had two menstrual bleeding episodes and 85 became pregnant. The remaining 696 women had only one (i.e., unconfirmed) menstrual bleeding episode before leaving the study (n = 150) or left the study before they had even one bleeding episode (n = 546).

Table 1 shows the distribution of the 85 pregnancies that occurred during the study according to study center, breast-feeding status at the estimated time of conception, and use of a family planning method at the estimated time of conception. One third of all pregnancies reported in the study

**TABLE 2**

Number of pregnancies during (versus after) amenorrhea among breast-feeding women who were not using contraception according to four definitions of the end of amenorrhea, by study center.

| | End of amenorrhea* according to the indicated definition | | | | |
|---|---|---|---|---|---|
| | HRP rule | | | | |
| Study center | Confirmed first menses during amenorrhea (after amenorrhea) | All first menses during amenorrhea (after amenorrhea) | Woman's perception of first menses during amenorrhea (after amenorrhea) | First reported bleeding episode during amenorrhea (after amenorrhea) | Total† |
| Chengdu | 18 | 15 | 16 | 15 | 20 |
| | (2) | (5) | (4) | (5) | |
| Guatemala City | 4 | 3 | 4 | 3 | 9 |
| | (5) | (6) | (5) | (6) | |
| Melbourne/Sydney | 2 | 2 | 5 | 2 | 5 |
| | (3) | (3) | (0) | (3) | |
| New Delhi | 2 | 1 | 2 | 1 | 5 |
| | (3) | (4) | (3) | (4) | |
| Sagamu | 0 | 0 | 0 | 0 | 0 |
| | (0) | (0) | (0) | (0) | |
| Santiago | 1 | 0 | 1 | 0 | 2 |
| | (1) | (2) | (1) | (2) | |
| Uppsala | 4 | 4 | 4 | 4 | 5 |
| | (1) | (1) | (1) | (1) | |
| All centers | 31 | 25 | 32 | 25 | 46 |
| | (15) | (21) | (14) | (21) | |

*Note:* HRP = human reproduction programme.

* See text for definitions.

† Total number of breast-feeding women who were not using contraception at the estimated time of conception.

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occurred in one center (Chengdu). Twenty-one women conceived after the infant had been totally weaned, leaving 64 women who became pregnant during breast-feeding. The cases of pregnancy after weaning are not considered further, as the focus of this analysis is pregnancy during lactation.

Among the 64 pregnancies that occurred during lactation, one fourth (n = 16) occurred during full breast-feeding and three fourths (n = 48) occurred when the infant was receiving caloric food supplements of varying amounts (i.e., during partial breast-feeding). Nearly all the pregnancies that occurred during full breast-feeding (15 of the 16) were in one center (Chengdu).

Among the 64 women who conceived while breast-feeding, 18 reported using a family planning method during the estimated time of conception, leaving 46 pregnancies that occurred among breast-feeding women who were not using contraception. Contraceptive failure was associated with the use of withdrawal, natural methods of family planning, barrier methods, intrauterine devices, and vasectomy. About half the contraceptive failures occurred after the women clearly were already cycling (i.e., menstruating by the confirmed first menses—HRP rule).

## Conceptions During Lactational Amenorrhea

Table 2 shows the distribution of the 46 pregnancies that occurred among breast-feeding women who were not using contraception according to whether the pregnancy occurred during amenorrhea as per each of the four definitions of the end of amenorrhea. When the confirmed first menses—HRP rule was used to define the end of amenorrhea, 31 pregnancies (67%) among breast-feeding women who were not using contraception occurred during amenorrhea. However, when all first menses—HRP rule or first reported bleeding episode was used to define the end of amenorrhea, only 25 pregnancies (54%) occurred during amenorrhea. This is to be expected, because when bleeding episodes that are not confirmed to be cyclic mark the end of amenorrhea, the period of amenorrhea is shortened.

When the end of amenorrhea was defined as the woman's perception of the first menses, the number of pregnancies that occurred during amenorrhea was almost the same as when the confirmed first menses rule was used. However, this is just a coincidence because the women who became pregnant during amenorrhea are somewhat different under the two definitions. Women frequently reported vaginal bleeding episodes that they did not describe as normal menses.

**TABLE 3**

Six-month cumulative pregnancy rates during lactational amenorrhea up to the end of full breast-feeding.

| | End of amenorrhea according to the indicated definition | | | |
|---|---|---|---|---|
| | HRP rule | | | |
| Study center | Confirmed first menses only | All first menses | Woman's perception | First reported bleeding episode |
| Chengdu | 1.8 (0–3.5) | 1.4 (0–2.9) | 1.4 (0–2.9) | 1.4 (0–3.0) |
| Woman-months | 1,390 | 1,388 | 1,374 | 1,364 |
| Guatemala City | 0 | 0 | 0 | 0 |
| Woman-months | 93 | 93 | 88 | 86 |
| Melbourne/Sydney | 0 | 0 | 0 | 0 |
| Woman-months | 742 | 742 | 753 | 707 |
| New Delhi | 0 | 0 | 0 | 0 |
| Woman-months | 356 | 353 | 327 | 307 |
| Saganu | 0 | 0 | 0 | 0 |
| Woman-months | 13 | 13 | 13 | 13 |
| Santiago | 0 | 0 | 0 | 0 |
| Woman-months | 78 | 78 | 79 | 70 |
| Uppsala | 0 | 0 | 0 | 0 |
| Woman-months | 297 | 296 | 305 | 284 |
| All centers | 1.2 (0–2.4) | 0.9 (0–2.0) | 0.9 (0–2.0) | 1.0 (0–2.1) |
| Woman-months | 2,969 | 2,963 | 2,939 | 2,831 |

*Note:* Values are percentages, with 95% confidence intervals in parentheses. Cumulative pregnancy rates were censored at the initiation of contraception and adjusted for exposure to coitus during each fortnight. HRP = Human Reproduction Programme.

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## Rates of Pregnancy During Lactational Amenorrhea

Cumulative pregnancy rates at 6 months after childbirth during lactational amenorrhea up to the end of full and partial breast-feeding are shown in Tables 3 and 4, respectively. The corresponding rates at 12 months after childbirth are shown in Tables 5 and 6. The breast-feeding categories are used cumulatively so that, for example, for all centers combined, in the 6-month life table using the confirmed first menses definition, the 5,639 woman-months of exposure up to the end of partial breast-feeding (Table 4) includes the 2,969 months of exposure during full breast-feeding in Table 3.

### *All Centers Combined*

For all centers combined, women who were still breast-feeding and remained amenorrheic (according to the HRP-confirmed first menses definition) at the end of 6 months had a cumulative pregnancy rate of 0.8% (95% confidence interval [CI] = 0.2%–1.4%), whereas at the end of 12 months, they had a cumulative pregnancy rate of 4.4% (95% CI = 2.5%–6.3%).

The cumulative pregnancy rates calculated from delivery until the end of full breast-feeding and from delivery until the end of partial breast-feeding were not significantly different ($P<.05$) at either time limit (6 or 12 months). However, for each breast-feeding status, the pregnancy rate at 12 months postpartum was substantially higher than that at 6 months postpartum.

There were no statistically significant differences in pregnancy rates among the various definitions of the end of amenorrhea at either 6 or 12 months. Although the various definitions of the end of amenorrhea yielded different numbers of women who became pregnant before the return of menses (Table 2), these different numerators did not result in significantly different rates of pregnancy.

### *Center Differences*

Among the individual centers, as seen in Tables 3 and 5, there were no pregnancies during amenorrhea and full breast-feeding in any center except Chengdu. Thus, the pregnancy rates during full breast-feeding are entirely a reflection of one center.

The 6-month pregnancy rate during partial breast-feeding and lactational amenorrhea was notably high in Uppsala at 3.2% (95% CI = 0%–7.8%). No pregnancies were reported in the other developed country (Melbourne/Sydney) under these conditions.

In Santiago, no pregnancies were reported during amenorrhea except when amenorrhea was defined according to the woman's perception. Using the woman's perception of the first menses, the pregnancy rate during partial breast-feeding

## TABLE 4

Six-month cumulative pregnancy rates during lactational amenorrhea up to the end of partial breast-feeding.

| | End of amenorrhea according to the indicated definition | | | |
|---|---|---|---|---|
| | HRP rule | | | |
| Study center | Confirmed first menses only | All first menses | Woman's perception | First reported bleeding episode |
| Chengdu | 1.1 (0–2.2) | 0.9 (0–1.8) | 0.9 (0–1.9) | 0.9 (0–1.9) |
| Woman-months | 1,937 | 1,934 | 1,910 | 1,900 |
| Guatemala City | 0.7 (0–2.1) | 0.7 (0–2.2) | 0.7 (0–2.2) | 0.8 (0–2.5) |
| Woman-months | 812 | 799 | 801 | 723 |
| Melbourne/Sydney | 0 | 0 | 0 | 0 |
| Woman-months | 1,109 | 1,109 | 1,131 | 1,053 |
| New Delhi | 0 | 0 | 0 | 0 |
| Woman-months | 731 | 721 | 665 | 610 |
| Sagamu | 0 | 0 | 0 | 0 |
| Woman-months | 281 | 281 | 277 | 272 |
| Santiago | 0 | 0 | 4.3 (0–12.4) | 0 |
| Woman-months | 258 | 254 | 263 | 229 |
| Uppsala | 3.2 (0–7.8) | 3.2 (0–7.8) | 3.1 (0–7.4) | 3.5 (0–8.4) |
| Woman-months | 511 | 511 | 521 | 481 |
| All centers | 0.8 (0.2–1.4) | 0.7 (0.1–1.3) | 0.8 (0.2–1.4) | 0.8 (0.1–1.4) |
| Woman-months | 5,639 | 5,609 | 5,568 | 5,268 |

*Note:* Values are percentages, with 95% confidence intervals in parentheses. Cumulative pregnancy rates were censored at the initiation of contraception and adjusted for exposure to coitus during each fortnight. HRP = Human Reproduction Programme.

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## TABLE 5

Twelve-month cumulative pregnancy rates during lactational amenorrhea up to the end of full breast-feeding.

| | End of amenorrhea according to the indicated definition | | | |
|---|---|---|---|---|
| | HRP rule | | | |
| Study center | Confirmed first menses only | All first menses | Woman's perception | First reported bleeding episode |
| Chengdu | 7.8 (2.7–12.9) | 7.4 (2.4–12.5) | 8.4 (3.0–13.7) | 7.7 (2.5–13) |
| Woman-months | 1,706 | 1,704 | 1,682 | 1,669 |
| Guatemala City | 0 | 0 | 0 | 0 |
| Woman-months | 95 | 95 | 90 | 88 |
| Melbourne/Sydney | 0 | 0 | 0 | 0 |
| Woman-months | 762 | 761 | 772 | 725 |
| New Delhi | 0 | 0 | 0 | 0 |
| Woman-months | 362 | 358 | 331 | 309 |
| Sagamu | 0 | 0 | 0 | 0 |
| Woman-months | 13 | 13 | 13 | 13 |
| Santiago | 0 | 0 | 0 | 0 |
| Woman-months | 79 | 79 | 80 | 73 |
| Uppsala | 0 | 0 | 0 | 0 |
| Woman-months | 298 | 298 | 307 | 285 |
| All centers | 6.8 (2.1–11.5) | 6.6 (1.9–11.2) | 7.4 (2.5–12.3) | 6.9 (2.0–11.8) |
| Woman-months | 3,315 | 3,308 | 3,275 | 3,162 |

*Note:* Values are percentages, with 95% confidence intervals in parentheses. Cumulative pregnancy rates are censored at the initiation of contraception and adjusted for exposure to coitus during each fortnight. HRP = Human Reproduction Programme.

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**TABLE 6**

Twelve-month cumulative pregnancy rates during lactational amenorrhea up to the end of partial breast-feeding.

| | End of amenorrhea according to the indicated definition | | | |
|---|---|---|---|---|
| | HRP rule | | | |
| Study center | Confirmed first menses only | All first menses | Woman's perception | First reported bleeding episode |
| Chengdu | 5.8 (2.7–8.8) | 5.1 (2.2–8) | 5.6 (2.5–8.7) | 5.3 (2.3–8.3) |
| Woman-months | 2,934 | 2,930 | 2,867 | 2,844 |
| Guatemala City | 4.2 (0–9.1) | 2.3 (0–5.8) | 6 (0–12) | 2.8 (0–6.8) |
| Woman-months | 1,159 | 1,132 | 1,128 | 998 |
| Melbourne/Sydney | 2.6 (0–7.6) | 2.6 (0–7.7) | 5.3 (0–11.4) | 2.8 (0–8.3) |
| Woman-months | 1,517 | 1,517 | 1,556 | 1,427 |
| New Delhi | 5.5 (0–13.4) | 3.8 (0–11) | 6.5 (0–15.8) | 4.8 (0–13.9) |
| Woman-months | 960 | 950 | 854 | 788 |
| Sagamu | 0 | 0 | 0 | 0 |
| Woman-months | 506 | 504 | 486 | 480 |
| Santiago | 0 | 0 | 4.3 (0–12.4) | 0 |
| Woman-months | 323 | 313 | 326 | 271 |
| Uppsala | 5.4 (0–11.6) | 5.4 (0–11.6) | 5.2 (0–11) | 5.9 (0–12.6) |
| Woman-months | 634 | 633 | 652 | 599 |
| All centers | 4.4 (2.5–6.3) | 3.7 (1.9–5.5) | 5.2 (3.1–7.4) | 4.1 (2.1–6.1) |
| Woman-months | 8,033 | 7,979 | 7,869 | 7,407 |

*Note:* Values are percentages, with 95% confidence intervals in parentheses. Cumulative pregnancy rates are censored at the initiation of contraception and adjusted for exposure to coitus during each fortnight. HRP = Human Reproduction Programme.

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and amenorrhea was 4.3% at both 6 and 12 months (95% CI = 0%–12.4%).

## Resumption of Sexual Relations

In all centers except Sagamu, women started having intercourse on average when the infant was about 6–8 weeks old (Table 7). In Sagamu, where a period of postpartum abstinence is traditional, the median time for the resumption of intercourse was >17 weeks postpartum. Women were not asked how often they had intercourse but simply whether it had occurred since the previous follow-up visit. Women in Chengdu reported intercourse significantly more often ($P<.001$) than women in any other center: intercourse was reported during >82% of the follow-up interviews.

## Use of Contraception

Women who intended to use a hormonal method of contraception after childbirth were not recruited to the study and those who started to use hormonal contraception during the course of the study (n = 107) were discontinued. For those women who initiated the use of nonhormonal contraception during amenorrhea, the median time to the start of contraceptive use is shown in Table 8. In Uppsala and Melbourne/Sydney, >70% of these women started using a barrier method of contraception, as did >50% of the women in Guatemala City, New Delhi, and Sagamu. More than 90% of these women in Santiago and 48% in Chengdu used an intrauterine device. Female sterilization was common in New Delhi (26.4%) and Guatemala City (11%), whereas in Chengdu, the partners of 50% of the women who initiated the use of contraception during the study underwent vasectomy. Withdrawal was used commonly in Sagamu (29.4%), Guatemala City (11.7%), and Uppsala (9.9%).

**TABLE 7**

Median time to the start of intercourse and percentage of 2-week intervals during which intercourse occurred since admission to the study and since the start of intercourse, by center.

| | Median time to the start of intercourse | | Percentage of 2-week intervals during which intercourse occurred | |
|---|---|---|---|---|
| Study center | No. of days | 95% confidence interval | Since admission to study | Since resumption of coitus |
| Chengdu | 42 | 40.9–43.1 | 82.1 | 99.2 |
| Guatemala City | 40 | 38–41.5 | 58.4 | 80.6 |
| Melbourne/Sydney | 52 | 51.5–53 | 69.3 | 81.7 |
| New Delhi | 52 | 51–52 | 62.4 | 92.4 |
| Sagamu | 122 | 108–137 | 47.5 | 81.0 |
| Santiago | 51 | 50.5–52 | 62.1 | 86.2 |
| Uppsala | 53 | 51–54 | 61.2 | 79.5 |

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**TABLE 8**

Percentage of women who were not using contraception before their first menses and the median time to the initiation of contraceptive use among users, by study center.

| Study center | Percentage of women who were not using contraception | Median time to initiation of contraceptive use | |
|---|---|---|---|
| | | No. of days | 95% CI |
| Chengdu | 68.4 | 126 | 110–165 |
| Guatemala City | 58.1 | 52 | 51–53 |
| Melbourne/Sydney | 46.3 | 51 | 48–56 |
| New Delhi | 61.7 | 44 | 39–52 |
| Sagamu | 59.4 | 81 | 79–93 |
| Santiago | 17.2 | 39 | 39–40 |
| Uppsala | 31.3 | 56 | 55–68 |

*Note:* The first menses was defined as the confirmed first menses—Human Reproduction Programme rule. CI = confidence interval.

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## DISCUSSION

Pregnancy rates during lactational amenorrhea of 5%–10% (without regard for time postpartum) have been reported consistently in demographic studies (13, 14). Estimates of the risk of pregnancy during amenorrhea calculated from ovulation rates have varied from 0.9% (15) to 1.7% (16) at 6 months, figures that are in close agreement with the findings of this study. In this study, the cumulative pregnancy rates ranged from 3.7% (95% CI = 1.9%–5.5%) to 7.4% (95% CI = 2.5%–12.3%) among amenorrheic women at 12 months, findings that are in agreement with the estimate of 7% made by Short et al. (16) in a study of Australian women, but lower than the estimate of 17.2% made by Diaz et al. (15) in a study of women from Santiago, Chile.

The overall rates of pregnancy observed herein during lactational amenorrhea until the end of full breast-feeding did not differ significantly from those until the end of partial breast-feeding, at either 6 or 12 months. The pregnancy rate had been expected to increase from the full to the partial category of breast-feeding because previous research linked breast-feeding frequency and the delay of supplementation to the duration of lactational infertility. The dose-response was not seen when the centers were combined because of the pregnancies that occurred during lactational amenorrhea in the full breast-feeding category (all of which occurred in Chengdu).

Mothers in Chengdu were more sexually active and avoided supplementing for a longer period than generally recommended; this period was longer than that in all the other centers. However, actual breast-feeding behavior in Chengdu during full breast-feeding appeared to be reduced compared with the other centers (11). The mean total duration of suckling was lowest in Chengdu during the first 6 postpartum months, and at no time during amenorrhea did infants in Chengdu spend more than a mean total duration of 80 minutes per day at the breast (11).

Some investigators (17, 18) have suggested that there may be a threshold for suckling duration per day that is required for nipple stimulation to maintain suppression of the hypothalamic-pituitary axis, and that when suckling duration falls below this threshold, the risk of ovulation and therefore of pregnancy increases. Finally, it is important to remember that the breast-feeding status reported here (i.e., full or partial breast-feeding) is actually an index of the degree to which the infants were given supplements and not some amount of breast-feeding (see definition). Thus, this analysis more accurately supports conclusions about how much supplementation can be tolerated than about how much breast-feeding stimulation is required.

The comparatively high 6-month pregnancy rate seen in Uppsala during amenorrhea and partial breast-feeding was characterized by a wide confidence interval because of the comparatively small number of woman-months of exposure. In Melbourne, the closest comparison group, no pregnancies occurred under the same conditions and the exposure time was nearly double that in Uppsala.

The pregnancies seen in Santiago only when the woman's perception of the first menses was used to define the end of amenorrhea suggests that this somewhat subjective measure of the return of menses may not be appropriate for use with the LAM. All the other definitions applied in Santiago resulted in pregnancy rates during amenorrhea of zero. As in Uppsala, the confidence interval of the pregnancy rate was wide, owing at least in part to the small number of woman-months of exposure.

Small numbers of woman-months of exposure to pregnancy were seen in Sagamu and in Santiago. These were due to censoring for lack of sexual activity and for contraceptive use, respectively.

Care was taken in this study to define the end of amenorrhea carefully and to consider whether any one definition of the first menses would be associated with a higher or lower rate of pregnancy during amenorrhea; however, no difference in the rate of pregnancy during lactational amenorrhea was found when the various definitions were compared. Thus, although a careful interpretation of the meaning of a bleeding episode (i.e., the HRP-confirmed first menses) resulted in a longer duration of amenorrhea and a correspondingly higher number of pregnancies, the corresponding pregnancy rate was not significantly higher than when a simpler definition of menses (i.e., the first reported bleeding episode) was used. By the latter, simpler definition, the duration of amenorrhea is shorter, and more months of unnecessary contraceptive use would result if women started

to use contraception at the end of amenorrhea. However, the simpler definition may have more programmatic and personal acceptability, and women may find double protection to be acceptable in the face of early unexplained bleeding episodes. In this discussion, however, the illustrations of the pregnancy rates generally use the HRP-confirmed first menses to define the end of amenorrhea because this definition resulted in the greatest period of exposure to pregnancy during amenorrhea, presenting a "worst-case" scenario.

The Bellagio Consensus (4, 5) led to the development of the LAM of family planning (9), which advises that a woman has a cumulative risk of pregnancy of <2% if she is amenorrheic and fully or nearly fully breast-feeding as long as the infant is still <6 months old. If any of these three conditions is not met, she is advised to use a method of family planning that does not interfere with breast-feeding. For all centers combined, the highest 6-month cumulative pregnancy rate among women who were fully breast-feeding, amenorrheic, and not using contraception in this multicenter study was 1.2% (95% CI = 0%–2.4%). Thus, this study confirms the Bellagio Consensus (19).

It is important to note that the women in this study were not using the LAM. Indeed, the method had not been created until after this study was begun. Women who are proactively trying to avoid pregnancy through good breast-feeding practices and the recognition of the return of menses may behave differently than women who are simply breast-feeding their infants. Therefore, the efficacy of the LAM is only simulated in this study.

However, it can be argued that the efficacy of the LAM would be better in actual use than in simulated analyses of observed breast-feeding behaviors because users of the LAM learn the breast-feeding behaviors that maximize milk production (and, simultaneously, the duration of lactational amenorrhea) when they learn the LAM algorithm (9). The fact that contemporary breast-feeding practices were studied herein (i.e., there was no attempt to change existing breast-feeding behaviors) suggests that the rates produced may underestimate the pregnancy protection during actual use of the LAM.

The extent to which women in this study represent likely LAM users is not clear. All mothers previously had breastfed an infant for at least 4 months and intended to breast-feed the study infant for at least 6 months. To date, the studies of LAM efficacy suffer from the drawback of including only women with breast-feeding experience. It is reasonable to characterize typical LAM users as women who intend to breast-feed for at least 6 months, but the effect of previous breast-feeding experience on current LAM performance is unknown.

Short et al. (16) recommended extending the Bellagio or LAM guidelines for populations with a long duration of breast-feeding, suggesting that, provided women remained amenorrheic and continued to breast-feed, the method could give good protection for up to 12 months after childbirth irrespective of when supplements are introduced. In this study, the highest 12-month pregnancy rate among the amenorrheic women who were not using contraception was 7.4% (95% CI = 2.5%–12.3%). The range of the CI suggests that although attempts to extend the LAM beyond 6 months in the presence of some degree of supplementation (provided that amenorrhea persists) may be possible, they should be made with caution because more pregnancies can be expected than would be seen with LAM use for only 6 months, as determined in the original Bellagio Consensus (4, 5).

The period of lactational amenorrhea is characterized by a profound degree of protection from pregnancy. Although the suckling stimulus drives the neuroendocrinologic mechanism of lactational infertility, the degree of supplementation to breast-feeding in this study did not yield a dose-response in the pregnancy rate, probably because of the prolonged duration of full breast-feeding in one center that accounted for all the pregnancies that occurred during full breast-feeding in amenorrheic women.

Regardless of the degree of supplementation, the pregnancy rate increased with time from the 6th to the 12th month postpartum. Overall, the rate of pregnancy during amenorrhea was unaffected by variations in the definition of the return of menses. This large, multicenter study found that the cumulative 6-month rate of pregnancy during lactational amenorrhea was between 0.8% (95% CI = 0.1%–1.4%) and 1.2% (95% CI = 0%–2.4%). This is equivalent to the protection provided by many nonpermanent contraceptive methods as they are actually used and upholds the 1988 Bellagio Consensus.

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## APPENDIX A

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# Oral progestogen-only contraception may protect against loss of bone mass in breast-feeding women

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## Summary

**BACKGROUND AND OBJECTIVES A worldwide trend towards increasing life expectancy has meant that osteoporosis is emerging as an important public health problem. The loss of bone mineral density and its restoration in association with a premenopausal but physiological hypo-oestrogenic state may serve as an important model for research into the pathogenesis and prevention of osteoporosis. With this in mind we have undertaken a longitudinal study of changes in bone mineral density over one year in women after childbirth.**

**DESIGN Observational study of 31 women in the first year following childbirth; 11 intending to breast-feed and use barrier methods of contraception, 9 intending to breast-feed and to use the progestogen-only pill and 10 intending to artificially feed and to use barrier methods.**

**PATIENTS Recruitment was from the antenatal clinics of the Simpson Memorial Maternity Pavilion. Only non-smokers who had regular menstrual cycles prior to conception were included .**

**MEASUREMENTS Bone mineral density was measured at the lumbar spine within 3 weeks of childbirth and repeated at 6 and 12 months post partum. Plasma oestradiol, prolactin and osteocalcin concentrations were measured at each visit.**

**RESULTS Breast-feeding women using barrier methods lost a mean ± SE of 4·9 ± 1·5% of bone mineral density in the first 6 months following delivery. This was however reversible since by one year the bone mineral density was no different from that measured immediately post partum. Breast-feeding women using the progestogen-only pill lost a significantly smaller percentage of bone mineral density in 6 months and by one year bone mineral density was 2·95 ± 0·75% higher than post partum. Artificially feeding women had a steady increase in bone mineral density in the first year and bone mineral density was on average 4·3 ± 1·2% higher.**

**CONCLUSION Breast-feeding results in a reversible reduction in spinal bone mineral density. The small amounts of gestagen in the progesterone-only pill would appear to protect against this loss. The mechanism of this loss in bone mineral density and the potentially bone protective effects of gestagens require further study.**

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Premenopausal hypo-oestrogenic states (premature menopause, hyperprolactinaemic amenorrhoea (Schlechte *et al.*, 1992) and hypogonadotrophic hypogonadism (Biller *et al.*, 1989)) are associated with a loss of bone mineral density. Lactation is associated with hypo-oestrogenism which may be prolonged in women who breast-feed their babies for a year or more, the norm in many developing countries. The evidence for a relation between bone mineral density (BMD) and lactation in humans is available from cross-sectional and longitudinal studies. Goldsmith and Johnston (1975) in a cross-sectional study in which the BMD of the radius was measured reported that bone mineral density was lower in women who had lactated in the past although this effect was less apparent in post-menopausal women, suggesting that the bone loss was reversible. In their study however, women were regarded as having lactated even if they had done so for a total of only two weeks. Wardlaw and Pike (1986) in a similar cross-sectional study measuring BMD at the radius suggested that BMD was reduced in women with longer periods of lactation. In a prospective study, Hayslip and colleagues (1989) described bone mineral loss from the spine, but not from the forearm, during the first 6 months post partum in lactating women but not in women who did not breast-feed. Bone mineral density was not measured after weaning and no account was taken of ovarian activity. Kent and co-workers (1990) also described bone loss in lactating women and reported the restoration of normal bone mineral density after weaning; however, in their study BMD was measured in the forearm and no mention was

made of ovarian activity. More recently, Sowers *et al.* (1993) demonstrated a reversible reduction in BMD at spine as measured by dual-energy X-ray absorptiometry with lactation exceeding 5 months duration.

Menopause related bone loss is a direct consequence of oestrogen deficiency and can be prevented by the administration of exogenous oestrogens (Lindsay *et al.*, 1976). It has been suggested that progesterone may also be involved in bone metabolism. Oestrogen receptors are present in osteoblasts whereas it is thought that progesterone receptors are 'induced' only in the presence of oestrogen (Eriksen *et al.*, 1988). Mandel *et al.* (1982) found that bone resorption (as assessed indirectly by a reduction in the urinary excretion of calcium and hydroxyproline) was inhibited by medroxyprogesterone acetate. In contrast, Gallagher *et al.* (1991) found that medroxyprogesterone acetate failed to prevent postmenopausal bone loss as assessed by direct measurement of spinal and radial bone density.

We were interested to observe changes in bone mass which may occur during lactation and, in addition, to observe the effect of progesterone as commonly used in the minipill for contraception during this time. With this in mind we undertook a longitudinal study of changes in bone mineral density over one year in women after childbirth.

### Subjects

Thirty-one women were recruited from the post-natal wards of the Simpson Memorial Maternity Pavilion in Edinburgh. All had regular menstrual cycles prior to conception and had no significant past medical history. None of the women were smokers. Twenty-one were intending to breast-feed their infants for at least 6 months. Of these, 12 planned to use barrier methods of contraception (group A) while 9 intended to use the progestogen-only pill (POP) (group B). Of these, 3 used Noriday (0·35 mg norethisterone) and 6 used Microval (0·3 mg levonorgesterol). Ten women intending to artificially feed and to use a barrier method were also recruited (group C).

A simple dietary history, including alcohol intake, was recorded. Vegetarians and women regularly using vitamin or calcium supplements were excluded from the study. All the women were judged to have a daily calcium intake of about 800 mg. Exercise patterns before pregnancy were noted on admission to the study and women with a history of regular strenuous exercise, e.g. marathon running, were excluded. Height and weight and, in the case of the breast-feeding mothers, suckling frequency, were recorded at every visit and blood was taken for the measurement of calcium, phosphate, albumin, alkaline phosphatase, osteocalcin (except group B, the assay was no longer available), prolactin and oestradiol. All participants kept a note of the date of their first menstrual period post partum.

Bone mineral density (BMD) was measured by dual-energy X-ray absorptiometry (DEXA) using a Hologic QDR 1000 densitometer (Hologic Inc., Waltham, USA). Half-way through the study this was exchanged for a whole body version of the same system (QDR 1000W). The second system was cross-calibrated by the manufacturer to give the same BMD as the first for an anthropometric spine phantom. There was no significant change in phantom BMD during the entire period of the study. The mean difference in phantom BMD between the two systems was only 0·01% and the coefficient of variation during the entire study period 0·31%. In addition, measurements performed on a group of subjects on both systems gave a mean coefficient of variation of 0·65% which was not significantly different from repeat measurements performed using the same instrument. Therefore for the purpose of the present study the two instruments were essentially identical. Bone mineral density of the lumbar spine was measured on three occasions in all women—within 4 weeks of delivery, and at 6 and 12 months post partum. The lumbar spine was chosen for its higher trabecular bone content and its excellent reproducibility (0·8%), in contrast to the femoral neck (1·46%). In addition, it was felt appropriate to keep the total visit time to a minimum since we were dealing with volunteers.

Calcium, phosphate, albumin and alkaline phosphate concentrations were measured at the time each sample was taken using a SMAC 2 analyser (Technicon) in the Department of Clinical Chemistry at the Royal Infirmary of Edinburgh. Oestradiol, prolactin and osteocalcin were measured in batches, samples having been separated and stored at −20°C. Oestradiol was measured by radioimmunoassay using the Clinical Incstar kit (Incstar Ltd). Interassay variation was 8% while intra-assay variation was 6%. Prolactin was measured by an in-house poly-monoclonal radiometric assay which used polyclonal antiserum from the Scottish Antibody Production Unit, Carluke and $^{125}$I-labelled monoclonal antibody from Netria, St Bartholomew's Hospital, London. The standard used was 83/573 (NIBSC) and inter and intra-assay variations were 8 and 5% respectively. Osteocalcin was measured in plasma using an in-house radioimmunoassay using antiserum raised in rabbits against bovine osteocalcin. $^{125}$I-labelled osteocalcin and the standards were prepared against bovine osteocalcin. The antisera cross-reacted with human osteocalcin. Inter and intra-assay variations were 12·1 and 4·5% respectively.

Full approval for the study was obtained from the Lothian Health Board Paediatrics/Reproductive Medicine Ethics of Medical Research Sub-Committee.

The data were normally distributed so mean, standard error and range are quoted. Analysis of variance with repeated measures was used to compare data between the groups of women and the changes over time.

**Results**

Not all of the breast-feeding women completed the study; one left the area after the first post partum BMD measurement and two women conceived during the study, neither of whom was scanned at 12 months. These results are not included in the analysis. The total number of breast-feeding women who completed the study was 18, 9 in each of the two groups A and B. All the artificial feeders finished the study (Group C). The characteristics of all three groups of mothers are shown in Table 1. For the purposes of the discussion the term breast-feeders will be used throughout for those women not using steroidal contraception (A), POP users for those using the progestogen-only pill (B) and artificial feeders (C) for the others.

All the women lost weight during the year of study and there was no difference in the rates of loss between groups. The mean fall from immediately post partum to six months was 4%, and from six to twelve months a further 2·6%.

*Bone mineral density*

The mean bone mineral densities of the spine in the immediate puerperium and at 6 and 12 months post partum for the three groups are shown in Table 2. The change in spinal BMD with time post partum is shown in Fig. 1 for each group. In all the breast-feeding women there was a fall in bone mineral density and this was significant as a group ($P < 0{\cdot}001$ Anova) between the immediate puerperium and 6 months post partum. In contrast, a fall in BMD occurred in only two bottle-feeding women over the same time period . From 6 to 12 months post partum, BMD rose significantly ($P < 0.001$) in the breast-feeding women. The absolute BMD at 12 months post partum was not significantly different from that measured within the first 4 weeks after delivery. There

**Table 1** Subject characteristics. Values are mean ± SE; range shown in parentheses. The groups are comparable with ANOVA except that the breast-feeders are significantly taller than the POP users

| Subject characteristics | Breast-feeders (A) ($n=9$) | POP users (B) ($n=9$) | Artificial feeders (C) ($n=10$) |
|---|---|---|---|
| Age (years) | 33·4 ± 1·25 (28–40) | 33·1 ± 1·2 (28–39) | 31·7 ± 1·2 (28–41) |
| Parity | 1·3 ± 0·21 (0–2) | 1·1 ± 0·1 (1–2) | 1·3 ± 0·21 (0–2) |
| Menarche (years) | 12·5 ± 0·37 (11–16) | 13·3 ± 0·55 (11–16) | 13·2 ± 0·35 (11–15) |
| Height (cm) | *169 ± 2 (155–179) | 162·3 ± 1·2 (157–169) | 166 ± 2 (156–176) |
| Weight post partum (kg) | 69·0 ± 2·2 (53·4–82·5) | 64·5 ± 4·0 (53·4–91·4) | 72·7 ± 3·5 (156–176) |
| Body mass index ($kg/m^2$) | 22·7 ± 0·12 (16·8–27·1) | 24·5 ± 0·16 (21·1–34·7) | 24·8 ± 0·13 (18·8–32·3) |

*$P < 0{\cdot}05$.

**Table 2** BMD ($g/cm^2$) at lumbar spine. Values are mean ± SE; range shown in parentheses. There is no difference between the groups at the first visit

| Time | BMD at spine ($g/cm^2$) Breast-feeders (A) | POP users (B) | Artificial feeders (C) |
|---|---|---|---|
| Post partum | 1·028 ± 0·03 (0·893–1·197) | 0·991 ± 0·04 (0·83–1·182) | 0·998 ± 0·025 (0·899–1·156) |
| 6 months | 0·976 ± 0·028** (0·884–1·112) | 0·977 ± 0·039* (0·803–1·141) | 1·02 ± 0·025 (0·859–1·122) |
| 12 months | 1·024 ± 0·025 (0·914–1·133) | 1·02 ± 0·04** (0·851–1·19) | 1·041 ± 0·027** (0·868–1·158) |

*$P < 0{\cdot}05$, **$P < 0{\cdot}01$ *vs* post-partum visit.

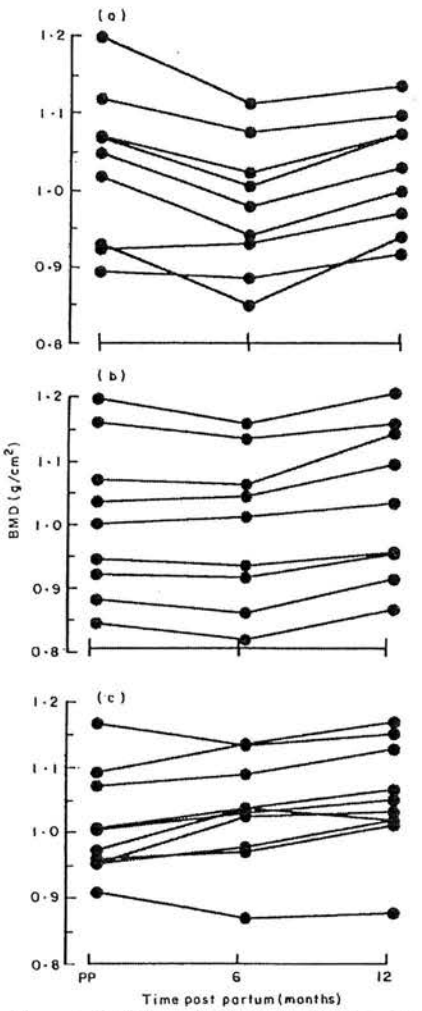


Fig. 1 Changes in BMD for each individual subject in a, group A (breast-feeders); b, group B (POP users); c, group C (artificial feeders).

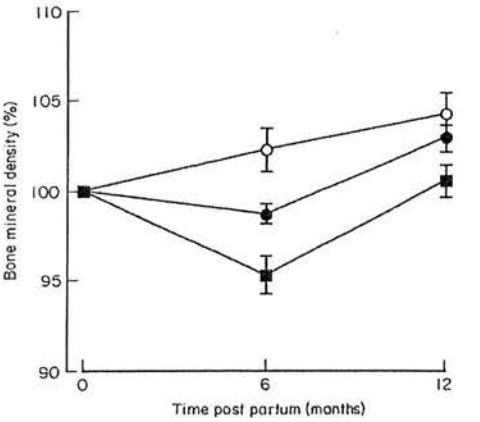


Fig. 2 Percentage changes in BMD ± SEM for each group. ■, Group A (breast-feeders); ●, group B (POP users); ○, group C, (artificial feeders).

appeared to be an overall increase in bone mineral density during the 12 months after childbirth in the bottle-feeding women. BMD was on average 4·3 ± 1·2% greater at 12 months post partum than within a month of delivery; this increase was statistically significant ($P < 0·01$). Seven of the nine POP users lost bone mass from delivery to 6 months (−1·4 ± 0·53%). This fall in BMD was overall significantly less than that seen in the breast-feeders ($P < 0·01$). From 6 to 12 months a significant increase did occur in POP users ($P < 0·005$). Overall BMD was significantly greater at 12 months (2·95 ± 0·75%) than at delivery ($P < 0·01$). Figure 2 shows the percentage change in each of the groups. It would therefore appear that some protection was afforded to bone mass by the use of the progestogen-only pill in breast-feeding women and that these POP users are better off at one year than the other breast-feeders.

The significant increase in BMD which occurred between 6 and 12 months post partum in the breast-feeding women appeared to be inversely related to the duration of amenorrhoea ($r = -0·6$) although this did not achieve significance. Menses returned at a median of 36 (range 23–41) weeks post partum. Thus all except one woman (who had only just menstruated) were still amenorrhoeic at 6 months post partum while all had resumed menses by the time BMD was measured again at 12 months. No correlation was noted in the POP users in whom menses returned at a median of 41 weeks. Menses returned at a median of 6·3 weeks (range 4–10) among the women who did not breast-feed.

### *Biochemical parameters*

Mean plasma oestradiol concentrations are shown in Table 3. At the first post-partum visit there was no difference

**Table 3** Plasma oestradiol, osteocalcin and alkaline phosphatase concentrations at each visit. Values are mean ± SE, range shown in parentheses

| | Breast-feeders (A) | | | POP users (B) | | | Artificial feeders (C) | | |
|---|---|---|---|---|---|---|---|---|---|
| Time of sampling | Oestradiol (pmol/l) | Osteocalcin (μg/l) | Alk phos (IU/l) | Oestradiol (pmol/l) | Osteocalcin (μg/l) | Alk phos (IU/l) | Oestradiol (pmol/l) | Osteocalcin (μg/l) | Alk phos (IU/l) |
| Post partum | 55 ± 3** (50–81) | 5·15 ± 2·10* (1·5–17·2) | 106 ± 9·8 (47–160) | 60·3 ± 6** (50–86) | na | 114 ± 13·8 (53–202) | 164 ± 33 (50–353) | 10·54 ± 0·98 (5·9–13·8) | 108 ± 11.58 (62–181) |
| 6 months | 132 ± 38 (60–357) | 12·2 ± 1*** (8·4–15·8) | 76·4 ± 8·6 (45–118)* | 145 ± 38 (50–423) | na | 83·5 ± 13 (33–160)* | 227 ± 81 (50–856) | 5·8 ± 1.13 (1·7–11·5) | 48·1 ± 4·05 (28–70) |
| 12 months | 199 ± 50 (50–443) | 7·47 ± 1·2** (2·6–13·3) | 73·8 ± 7·4 (42–108)* | 258 ± 77·6 (50–724) | na | 72·3 ± 13·9 (26–135)* | 167 ± 43 (50–451) | 3·67 ± 0·591 (2·0–8·5) | 53·9 ± 5·6 (36–95) |

Oestradiol: ** denotes $P < 0.01$ *vs* artificial feeders at post-partum visit and breast-feeders/POP users (A and B) at 6 months.
Osteocalcin: * denotes $P < 0.05$, ** denotes $P < 0.01$ and *** denotes $P < 0.001$ *vs* artificial feeders.
Alkaline phosphatase: * denotes $P < 0.05$ *vs* artificial feeders.

between groups A and B and these levels were significantly lower than in group C. All the women in groups A and B had oestradiol concentrations in the post-menopausal range. At the 6-month visit mean oestradiol concentration had increased in groups A and B and was not different from the artificial feeders (C). Serum prolactin concentrations were significantly higher in the early post-partum period among the breast-feeding mothers (A and B), 2319 ± 572 and 2278 ± 607 U/l respectively, than among the women who did not breast-feed (C) 291 ± 96 U/l. There was no relation between bone density changes and oestradiol concentrations.

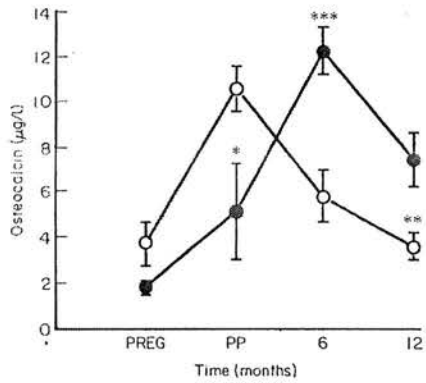


**Fig. 3** Plasma osteocalcin concentration ± SE in groups ○, A (breast-feeders) and ●, C (artificial feeders). *P*-values are shown for between group comparisons. *$P < 0.05$; **$P < 0.01$; ***$P < 0.001$.

Plasma osteocalcin concentrations increased in women in groups A and C between the third trimester of pregnancy and the early puerperium (Fig. 3). Concentrations were significantly higher ($P < 0.05$) among the bottle-feeding women than among breast-feeding women in the early post-partum weeks (Table 3, Fig. 3). By 6 months post partum osteocalcin was falling among the bottle-feeding women and the fall continued, so that by one year after delivery osteocalcin concentrations were no different from those measured during pregnancy. Among breast-feeding women however plasma osteocalcin concentrations continued to rise after delivery until by 6 months they were significantly higher ($P < 0.001$) than the values measured in the bottle-feeding women. Although osteocalcin concentrations fell between 6 and 12 months in breast-feeding women they remained elevated at one year after delivery when compared with concentrations measured in bottle-feeding women one year after childbirth ($P < 0.05$).

Alkaline phosphatase concentrations (Table 3) were elevated in the early post-partum period in all groups. In all groups of women alkaline phosphatase concentrations fell with time post partum but were still significantly elevated at 6 ($P < 0.01$) and 12 months ($P < 0.05$) in groups A and B when compared with artificially feeding women. No significant changes in either plasma phosphate or calcium concentrations were noted in either group of women.

## Discussion

It is clear from this study that lactation is associated with a significant, but reversible loss (4·3%) of bone mineral density during the first 6 months after childbirth. This loss would appear to be reduced by the use of the progestogen-

only contraceptive pill. Although BMD at the end of the study does not appear to differ between the three groups, the women studied lactated for relatively short periods compared to some other groups, for example in the Third World. In such women the situation may be quite different and therefore ultimately more clinically relevant. By 12 months post partum BMD is no different from that measured within 4 weeks of delivery in breast-feeding women. Interestingly, women who did not breast-feed or who used the progestogen-only pill (POP) appeared to have an increased bone mineral density at one year compared with that measured immediately post partum. Previous investigations of bone mineral content during pregnancy have shown contradictory results. Lamke *et al.* (1977) suggested that a fall in radial BMD occurred during pregnancy and this concurred with the finding by Drinkwater and Chesnut (1991) that both radial and femoral neck BMD fell. More recently, Sowers *et al.* (1993) recorded no change in femoral neck BMD in 32 women from preconception to post partum. In a second, as yet unreported, study we have measured BMD in the forearm of nine pregnant women early in the second trimester (14 weeks) and found no difference when the measurement was repeated within one month of delivery. Perhaps the fetal calcium load required (30 g for the skeleton) is not compensated by the increased gastrointestinal absorption and the decreased loss through the kidney. The use of the POP does not appear to affect circulating oestrogen so it is unlikely that this is the mechanism for the relative protection offered. It may simply be the presence of progestogen, albeit at small amounts, that offers this 'protection'. Norethisterone is itself relatively androgenic and may be bone protective. It is thought in addition that some gestagens may be metabolized to an oestrogen-like metabolite and this may explain our findings. Interestingly, Cundy and colleagues (1991) described significant loss of bone mass in women exposed for a mean of 10 years to the long-acting depot medroxyprogesterone acetate contraceptive, Depoprovera (DMPA). These women had low circulating concentrations of oestrogens. The number of subjects was small ($n=30$) but a later study (Cundy *et al.*, 1994) suggested that there was some recovery of BMD when DMPA was discontinued. Of course the effects of progestogens themselves may differ depending on whether they are given in oestrogen deficiency states or whether they induce oestrogen deficiency, as with the use of Depoprovera.

Our results suggest that the rate of recovery of bone mineral density during the second 6 months post partum in breast-feeding women may depend on the duration of amenorrhoea and thus on the duration of hypo-oestrogenism. The increase in BMD seen is similar to that seen when post-menopausal women are given oestrogen (Stevenson *et al.*, 1990). It would be interesting to repeat the study with a much larger number of women with a wide range of infant feeding patterns since the women in our study all tended to breast-feed and remain amenorrhoeic for a similar duration. A clearer relation might emerge in a group of women who had long periods of lactational amenorrhoea. In the United Kingdom most women introduce supplementary feeding when the infant is about 5 months of age. Suckling activity declines quite dramatically once supplements are started (Howie *et al.*, 1982) and the loss of BMD over the first 6 months may also be a function of the metabolic requirements for the production of milk. Elevated concentrations of plasma alkaline phosphatase and osteocalcin in breast as compared with bottle-feeding women also suggest increased bone turnover. The elevation of plasma osteocalcin may reflect the recovery of BMD to 'normal' by an increase in osteoblastic activity. In bottle-feeding women this was seen early in the puerperium, whilst in breast-feeders this was seen at 6 months, after which BMD increases. This was before the return of menstruation and after the introduction of solids in all except one woman suggesting that it may be the demands of milk production rather than hypo-oestrogenism that is the cause of bone loss.

As significant loss of bone mineral density appears to be a feature of lactation and would seem to be reversible we suggest that breast-feeding women may serve as an excellent model for the study of the relation between hormonal and nutritional factors in osteoporosis. This clear loss of bone mineral density should be taken into consideration by scientists working on new methods of contraception for lactating women because some methods, e.g. the analogues of GnRH (Fraser *et al.*, 1989), are themselves associated with bone loss.

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ORIGINAL RESEARCH ARTICLE

# Who Gives Advice About Postpartum Contraception?

Anna F. Glasier, Janet Logan,* and T.J. McGlew*

*Women were interviewed to determine what advice they received about postpartum contraception and what they thought of it. Only 4% of women discussed postpartum contraception antenatally. Up to 84% discussed the issue with a midwife on the postnatal ward but discussion was often felt to be brief, limited and frequently held as the mother was leaving the hospital. Obstetricians appeared to have little interest in the subject and only 50% of mothers left the hospital with supplies of a contraceptive. Almost all women discussed contraception with their general practitioner at the postnatal check but a significant number felt that the choice of method was limited to condoms or pills. The postnatal check is traditionally held at six weeks—two to three weeks after the recommended time for starting contraceptive precautions. Women with short inter-pregnancy intervals were younger, less likely to be married and more likely to default from postnatal follow-up. Pregnant women should be offered the opportunity during the antenatal period to discuss postpartum contraception with someone who has a special interest in the subject. The postnatal ward is not an appropriate setting for discussion about future contraception.* CONTRACEPTION 1996;53:217–220

KEY WORDS: contraception, postpartum, advice, interpregnancy interval

## Introduction

Almost all women in the United Kingdom receive high quality antenatal care from general practitioners (GPs), obstetricians and midwives but the postpartum period is relatively neglected. The UK Government's House of Commons Health Committee in its recent report on Maternity Services[1] concluded that postnatal care "is poorly evaluated and researched, delivered in often inappropriate and fragmented ways and has dissipated managerial focus which militates against efficient use of resources."

Included in postnatal care is the issue of postpartum contraception. Frequent contact with a variety of health care professionals during pregnancy and the puerperium provides numerous opportunities for discussion of future contraception. It is our impression, however, that the subject receives scant attention and is often less than adequately covered during the puerperium. For this reason we undertook a study to determine who gives women advice about contraception after childbirth, what women think of that advice and whether short inter-pregnancy intervals are related to lack of good advice about contraception.

## Materials and Methods

One-hundred-seventy-four women were recruited from a large Scottish teaching hospital delivering around 5500 women and undertaking some 2000 induced abortions each year. One-hundred women were selected randomly from the labour ward delivery lists; 50 (group A) were interviewed at home at eight weeks and 50 (group B) at one year after delivery. Mothers whose babies were in the Special Care Baby Unit were excluded. Forty women attending for antenatal care who had conceived within one year of childbirth (Group C) were interviewed at home before 28 weeks of pregnancy (women whose previous pregnancy had ended in a spontaneous miscarriage were excluded). Thirty-four women pregnant within one year of childbirth and seeking abortion (Group D) were interviewed after the request for abortion had been accepted but before the procedure was undertaken. There was no randomisation in Groups C and D, all women conceiving within one year of childbirth were invited to participate. Women who lived outside the City of Edinburgh or whose command of English was poor were excluded from recruitment to all groups. Women were told at the time of recruitment that they were taking part in a study about fertility after childbirth or abortion. The hospital staff were given the same information.

Semi-structured interviews covered socio-economic status, obstetric and contraceptive history, infant

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feeding plans, and advice received about contraception. The nature of the advice and whether or not it was seen by the woman to be appropriate or useful was determined.

Results were analysed using chi-square on SPSS.

## Results

Over 90% of women could recall clearly the nature of the advice given after childbirth and who gave it. Only one woman (in group B) was unable to recall whether she received any advice. There were no significant differences between the groups in the subjects' ability to recall the advice nor in the number of professionals giving advice suggesting that data collected from women one year after childbirth was reasonably accurate.

Women who had conceived within one year of a previous pregnancy and who planned to have the child (Group C) were younger (Table 1), less likely to be married or cohabiting and had fewer children than women who were not pregnant within one year of childbirth (Group B). None of these differences, however, reached a level of statistical significance. Women who had conceived again within one year but who opted for abortion (Group D) were the youngest group, had the most children but were the least likely to be married or cohabiting ($p<0.05$).

### *Advice Given Antenatally*

Only seven women (4%) remembered discussing contraception with a professional before the baby was born. Another five remembered contraception being mentioned in antenatal classes but in every case the advice was simply that breastfeeding could not be relied upon to prevent pregnancy.

### *Advice Given Postnatally*

Between 56% and 84% of women remembered a discussion with a midwife on the postnatal ward. Almost 50% of the women in each group had something negative to say about this discussion. The most common comment was that the discussion was approached as a necessary routine and sometimes undertaken with apparent reluctance. Discussion often took place as the mother and baby were being discharged from the ward and was part of the check list of topics to be covered at discharge, one woman said that a list was actually checked off. A total of 39 women (23 of them in group B) described the discussion as "unhelpful."

**Table 1.** Demographic details of the four groups interviewed after childbirth

| | Group A (n = 50) | Group B (n = 50) | Group C (n = 40) | Group D (n = 34) |
|---|---|---|---|---|
| Mean age (years) | 28.6 | 30.9 | 27.5 | 24.2 |
| Age range (years) | 19–41 | 18–42 | 17–40 | 17–37 |
| Married/ cohabiting | 48 | 47 | 39 | 17 |
| Single, living alone | 2 | 3 | 1 | 17 |
| First child | 22 | 24 | 9 | 12* |
| Second child | 21 | 20 | 9 | 15 |
| >Two children | 7 | 6 | 3 | 7 |

*Two women put their babies up for adoption.

Although midwives were the most likely professionals to raise the issue of infant feeding in relation to contraception—in group A 38% did so compared with only 4% of GPs—their repertoire of advice to women choosing to breastfeed appeared limited to progestogen-only pills (POP) or condoms. The contraceptive effects of breastfeeding were universally denied.

Doctors gave little advice on the postnatal wards. Only 8% of women in group B and 6% in Group D remembered talking to a doctor. Again, most of the comments about the quality of advice were negative.

Around 50% of women in each group left the hospital with supplies of a method except women in Group D, only 12 (35%) of whom were given supplies (all condoms).

Most women in group D were unable to recall whether or not contraception had been discussed during a home visit; however, between 20% (group C) and 58% (group A) of women could remember the topic of contraception being discussed during a home visit by the GP, midwife or health visitor. Almost without exception, midwives and health visitors raised the issue only to advise discussion with the GP.

Although the majority of women recalled discussion with the general practitioner—usually at the formal postnatal check six weeks after delivery—five in group A, four in group B and six in group C were adamant that they received no advice from the GP at anytime despite being seen in the doctor's office.

Some women chose not to attend a post-natal consultation. One in Group A and ten in Group D (29%) did not see their GP for a postnatal check. Two woman were already pregnant when they did attend (late) for consultation.

Twenty three-women in group C (almost 50%) and eight in group B were in some way dissatisfied with the discussion, seven of them claiming not to have been able to understand what was said. The commonest criticism of the GPs related to the lack of discussion about methods other than oral contraception or condoms. In both groups A and B, 46% of women started oral contraception postnatally while 32%

(group A) and 42% (group B) said they would use condoms.

Most women discussed contraception with at least two people, the commonest combination being the midwife on the postnatal ward and the GP. Almost half the women recalled discussions with at least three professionals and one woman in group C discussed her contraceptive plans with seven. In contrast, one woman in the same group claimed that she had never discussed contraception with anyone.

Only 2 of the 174 women were offered written information about contraceptive methods although a number commented that they would have liked some.

There were differences between the four groups of women in the source of advice. Women who had short inter-birth intervals were the least likely to have discussed contraception with a doctor on the postnatal ward and most likely to have missed out on, or avoided, discussion during the postnatal check. There was no statistically significant pattern of differences between women who had not conceived within one year and those with short interbirth intervals who had decided to continue with the pregnancy, but women who opted for abortion were significantly less likely to have discussed contraception with a hospital midwife or doctor or with their GP ($p<0.05$).

There were also significant differences in contraceptive behaviour at the time of conception (Table 2). Women in group C were less likely to have planned their pregnancy and significantly more likely ($p<0.05$) to have used no method of contraception than women in group A or B. Women in group C were least likely to have experienced failure of a method of contraception. More than half the women with short interpregnancy intervals who opted for abortion (group D) had used no method of contraception at the time of conception ($p<0.01$).

## Discussion

Despite the subject being raised by at least two professionals, many women found that they received little advice about postpartum contraception and a substantial minority complained that the advice they were given was limited. Only two out of 174 women volunteered a memory of a lengthy helpful discussion, one with a midwife and one with a GP.

**Table 2.** Circumstances surrounding conception, women after childbirth

| | Group A (%) | Group B (%) | Group C (%) | Group D (%) |
|---|---|---|---|---|
| Planned pregnancy | 64 | 62 | 55 | (60)* |
| No contraception | 16 | 24 | 30 | 56 |
| Method failure | 20 | 14 | 6 | 44 |

*60% of women in group D had planned the previous pregnancy; in all cases the index pregnancy was unplanned.

The postnatal ward is an inappropriate setting for contraceptive counselling. Mothers are discharged home after only three or four days and during their stay are anxious to establish infant feeding and to learn to care for the new baby. Midwives are good at these aspects of postnatal care but receive only limited training in family planning. For example, there appears to be a universal belief among midwives that breastfeeding does not prevent pregnancy despite numerous studies demonstrating that it does and a fairly recent consensus statement[2] reporting a 98% success rate for the contraceptive effects of lactational amenorrhoea. Contraception—indeed sex—is probably the last thing on a new mother's mind and to approach it as part of a routine check list at discharge is almost certainly a waste of time. Obstetricians very rarely, if ever, raise the topic of contraception in the antenatal clinic and once delivered, unless they are unwell, mothers are unlikely to see anyone except the most junior member of the medical staff who usually has a limited knowledge of contraception. Indeed, obstetricians have very little interest in postpartum contraception at all. In a recent review of the puerperium circulated to all fellows and members of the Royal College of Obstetricians and Gynaecologists[3] as the basis for a self-learning exercise, contraception was not mentioned although breast problems and depression (areas in which they might be thought to have less interest and expertise) were.

The onus currently falls on the GP. However, discussion is often delayed until the postnatal check which classically takes place at six weeks, at least two weeks after the recommended time for starting contraception. Despite many opportunities for doing so the GP rarely raises the topic of contraception during the pregnancy although it has been demonstrated that this is a useful strategy.[4]

Fair and Horsefall,[5] in a review of postnatal care in 77 training practices in South East Scotland (where the current study was undertaken), found that 100% of GPs discussed contraception at the postnatal consultation. Our study confirms that GPs rarely fail to discuss contraception at the postnatal check but suggests that a proportion of women find the discussion limited or perfunctory. At least two surveys of patients' experiences of postnatal care, one in Hertfordshire[6] and one in Grampian,[7] have suggested that many women are dissatisfied with the quality of postnatal care. While neither survey highlights the issue

of postpartum contraception, this would seem to be an area that needs attention.

In the United Kingdom, at least 30% of deliveries result from unplanned pregnancies[8] and substantial numbers of pregnancies end in induced abortion. Less than 70% of women in each of the groups we studied had actually planned to conceive. In addition, contraceptive failures accounted for a significant number of pregnancies and it is widely recognised that it is more often the user and not the method that fails. Many women in this study were using condoms—one of the less reliable methods of contraception—while very few used the more effective long-acting methods such as the IUD or depo-Provera.

We were unable to demonstrate in this study a statistically significant relationship between short interpregnancy intervals and poor contraceptive advice; nevertheless, there are suggestions that women who do conceive again after a short time are more likely to default from their postnatal checks and are likely to be young and unmarried. These high risk patients could be targeted by health care providers for more intensive discussions about family planning in its broadest sense. The antenatal and postnatal periods could offer an opportuinity to discuss not only the appropriateness of the chosen method of contraception but also its correct use.

Maternity care with its frequent exposure to health professionals offers a golden opportunity to discuss contraception at length. The topic should be raised antenatally when couples are not distracted by a new baby and when they have time to consider all the options. Moreover, it should be raised by someone who knows what they are talking about.

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ELSEVIER

Contraception

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Original research article

# Is postpartum contraceptive advice given antenatally of value?☆

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**Abstract**

In response to the concept that a good postpartum program should begin prenatally, this study was designed to determine whether the provision of expert contraceptive counseling during the antenatal period would have an impact on contraceptive uptake, patterns of contraceptive usage, and pregnancy rates during the first year after childbirth. Over 500 women attending antenatal clinics in each of three centers (Edinburgh, Scotland; Shanghai, People's Republic of China; Cape Town, South Africa) were randomized to receive expert contraceptive advice (participants, n = 771) or the standard advice routinely given in that setting (controls, n = 866). Follow-up was by postal or interviewer-administered questionnaires at 16 and 52 weeks after childbirth. There were no significant differences in the prevalence of contraceptive use at one year (over 79% in all centers) between participants and controls. In Edinburgh, participants were more likely to undergo sterilization ($p < 0.01$) than controls, otherwise there were no differences among Edinburgh, Shanghai, or Cape Town in either the methods of contraception chosen or in the methods used over time. Contraceptive counseling delivered antenatally appeared to have no impact on the pregnancy rate during the first year after childbirth. In Shanghai, over 11% of women in both groups underwent termination of pregnancy in the year of follow-up. In conclusion, although women in all centers said they found the opportunity to discuss contraception antenatally was useful, it had very little effect on contraceptive use or on subsequent pregnancy rates. 

*Keywords:* Contraception; Postpartum; Antenatal counseling

## 1. Introduction

Family planning providers have traditionally regarded the postpartum period as an opportunity for introducing and promoting contraception. In many developing countries special programs for the delivery of postpartum family planning services have been in existence since the 1960s [1]. In the UK, family doctors are paid to undertake a "postnatal check" for all postpartum women six weeks after childbirth, and almost all discuss contraception at that consultation [2]. A similar situation exists in Cape Town where women are seen during the first week postpartum and then referred for a later check to the local family planning clinic. In Shanghai, the emphasis is on antenatal care and there is no postnatal check.

Contraception—indeed sex—is probably the last thing on a new mother's mind during the first few days after delivery, yet leaving the discussion until later in the postpartum period may mean missing the opportunity altogether. Most women, even in the least developed countries, have some contact with health providers during their pregnancy, and yet the opportunity of giving advice about contraception during the antenatal period is often neglected. In a study of 174 women delivered at a large Scottish teaching hospital [2], only 4% discussed contraception antenatally, and advice given by a variety of health professionals after childbirth was often felt by the women to be inappropriate and insensitively timed.

In Cape Town, efforts are made in the antenatal clinics to raise awareness of postpartum contraception, usually in the form of group sessions led by the family planning advisors or clinic sisters. In Shanghai, all expectant mothers do attend antenatal courses, but the details given about contraceptive options available to them postpartum is limited.

In response to the concept that a good postpartum program should begin prenatally, we designed a study to determine whether the provision of expert contraceptive coun-

☆ The three centers in this study are part of the Contraceptive Development Network, which is funded by the Medical Research Council and the Department for International Development (G9523250).

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seling during the antenatal period would have an impact on contraceptive uptake, patterns of use, and pregnancy rates during the first year after childbirth. The study was undertaken by the Contraceptive Development Network in two developing countries, the People's Republic of China (Shanghai) and South Africa (Cape Town), and one developed country, Scotland (Edinburgh).

## 2. Participants and methods

In Edinburgh and Shanghai, women were recruited from a single large maternity hospital in each city. In Cape Town, recruitment was from three maternity obstetric units (MOU) outside the city in Guguletu, Mitchell's Plain, and Retreat, run by midwives providing a community-based antenatal and delivery service linked to secondary and tertiary hospitals. Recruitment started in the three centers between February and August 1997. In Edinburgh and Cape Town antenatal clinic sessions were randomized on a weekly basis (and on a daily basis in Shanghai) so that a single session contributed either all participants or all controls. Specialist (e.g., diabetic) antenatal clinics were excluded from the study.

Women were recruited into the study when they were between 24 and 36 weeks gestation. In Edinburgh, all women with appointments for a clinic randomized to provide controls received a letter informing them that, after childbirth, they would be sent a questionnaire designed to seek their views about certain aspects of their care. A study number was allocated when the letter was sent, thus a woman became a "control" simply by virtue of having an appointment for the antenatal clinic regardless of whether she attended or not. All women with appointments for a clinic randomized to contribute participants were sent a letter advising them that at an antenatal clinic appointment that took place between 24 and 36 weeks of pregnancy, they would have the opportunity to discuss plans for postpartum contraception with a specialist nurse. Women actively declining the offer were asked to return a "tear-off slip," and 37 women (14.5%) did so. In Shanghai and Cape Town women were recruited in person when they attended the antenatal clinic session, and a study number was allocated at that time. Sixty-three women refused to participate in Cape Town, and there were no refusals in Shanghai. Only demographic details and contact information were collected from control women, whereas participants received formal individual contraceptive counseling. In all centers, counseling was undertaken by a trained family planning nurse. Antenatal advice consultations for the participant group lasted up to 20 min and were tailored to the anticipated contraceptive needs of each individual woman who was then given appropriate written information to take home.

In all three cases, women allocated to the control group received the standard local care with regard to contraceptive advice. In Edinburgh contraception is not formally discussed at all during the antenatal period. Women are asked by a midwife about plans for contraception just before being discharged home with the new baby and, if appropriate, a limited supply of contraception (i.e., three condoms, one packet of contraceptive pills) is provided. Contraception is further discussed with the general practitioner at the routine postnatal check at around six weeks postpartum. In Shanghai postpartum contraception is discussed briefly during the group antenatal classes. Postpartum contraception may be discussed before discharge from the postnatal wards, but supplies of contraception are not usually given. Further advice may or may not be given thereafter by health care providers during the postpartum period. In Cape Town postpartum contraception is discussed during antenatal group sessions. Contraceptive advice is again given by the midwives or family planning advisors following delivery, and most women are offered Depo Provera before being discharged from hospital unless the patient has decided to have tubal ligation. During the postpartum period, nursing sisters at the baby clinics will inquire about contraception and advise when necessary.

All women were contacted at 16 weeks and 1 year after childbirth. In Edinburgh both questionnaires were sent by post, whereas in Shanghai a telephone interview was conducted at 16 weeks, and a questionnaire was sent by post at 52 weeks. Because many women in Cape Town were functionally illiterate and living in informal housing with unreliable mail deliveries, contact was made by telephone or personal visit, and the information was collected by interviewer-administered questionnaire. At 16 weeks, the questionnaire included demographic data; reproductive history; contraceptive use before the index pregnancy; plans for future pregnancies and contraception; details about who gave advice about postpartum contraception; and, for participants only, whether the expert family planning advice received at the antenatal clinic was found to be helpful. At one year after childbirth, women were asked for details of contraceptive use: currently and during the past year (using a monthly calendar), plans for future childbearing, and details of any pregnancies that had occurred since the index child was born.

In all centers, up to three further attempts were made to contact nonresponders (by letter, telephone, or attempted visit) before follow-up was abandoned.

### 2.1 Statistical analysis

By estimating a 10% pregnancy rate at one year after childbirth, it was calculated that a sample size of 600 participants and 600 controls would be required to detect a significant difference at the 5% level if antenatal counseling reduced the pregnancy rate to 5%. Anticipating a drop-out rate of up to 25% at one year, it was decided to recruit a total of 1500 women, 500 in each center, equally divided between controls and participants.

The two groups were compared by t-tests for quantitative

Table 1
Characteristics of the two study groups as derived from the 16-week questionnaire; figures are shown as mean ± SD or %

| | Edinburgh | | Shanghai | | Cape Town | |
|---|---|---|---|---|---|---|
| | Participants | Controls | Participants | Controls | Participants | Controls |
| Questionnaire returned (%) | 171 (67) | 214 (62) | 254 (98) | 263 (99) | 192 (75) | 197 (78) |
| Age (years) | 30 ± 6 | 31 ± 5 | 28 ± 4 | 28 ± 4 | 25 ± 5 | 25 ± 6 |
| Number of children | 1.8 ± 1 | 1.7 ± 1 | 1 | 1 | 1.9 ± 0.9 | 1.9 ± 1.1 |
| Marital status (%) | | | | | | |
| Married | 75 | 74 | 100 | 100 | 51 | 49 |
| Cohabiting | 19 | 20 | 0 | 0 | 8 | 7 |
| Single* | 6 | 6 | 0 | 0 | 41 | 44 |
| Partner's age (years) | 35 ± 11 | 35 ± 11 | 31 ± 4 | 32 ± 4 | 28 ± 6 | 29 ± 7 |
| Smoking, (%) | | | | | | |
| Never | 57 | 56 | 99.6 | 100 | 58 | 50 |
| Past | 21 | 29 | 0.4 | 0 | 1 | 3 |
| Now | 22 | 14 | 0 | 0 | 41 | 47 |
| Years education | 14 ± 3 | 14 ± 3 | 13 ± 2 | 13 ± 2 | 10 ± 2 | 10 ± 2 |
| Index pregnancy | | | | | | |
| Planned, (%) | 73 | 77 | 84 | 89 | 76 | 71 |
| Unplanned, (%) | 27 | 23 | 16 | 11 | 24 | 29 |
| Last contraception, % | | | | | | |
| Oral | 44 | 48 | 2 | 4 | 24 | 22 |
| Injectable | 1 | 4 | 0 | 0 | 39 | 43 |
| IUD | 2 | 1 | 0 | 0 | 1 | 2 |
| Condom | 42 | 37 | 35 | 31 | 1 | 1 |
| None | 5 | 5 | 43 | 50 | 35 | 33 |
| Other | 6 | 4 | 18 | 15 | 0 | 0 |

* A few women in Cape Town recorded "other" but because no details of partner were recorded they have been classified as single.

outcomes and chi-squared tests for categorized outcomes, using Yates' correction where appropriate.

## 3. Results

In all centers, delivery details were checked before first contact was made at 16 weeks after childbirth, and women who had experienced severe pregnancy complications (including stillbirth or neonatal death) were discontinued from the study. In addition, those who ultimately did not deliver at the study site were discontinued from the study, with the exception of Cape Town where participants continued to be followed-up if they had been referred to a secondary or tertiary hospital for delivery. A total of 506 women were recruited in Cape Town and 527 in Shanghai. In Edinburgh, many more women were allocated to the control group (simply by having an appointment for antenatal care) than to the participant group because the latter had to actually attend the antenatal clinic before being allocated a study number. In this center, 255 women (participants) received expert family planning advice at an antenatal clinic visit, whereas 349 women (controls) received a letter informing them that they would receive a questionnaire at some time after they had gone home from hospital.

Response rates for the 16-week follow-up, together with demographic details of the respondents, are shown in Table 1. There were no significant differences within any of the centers between participants and controls with respect to loss to follow-up. However, there were large differences between centers, with response rates varying from 62% in Edinburgh to 99% in Shanghai. There were some minor demographic differences between the three MOUs from which women were recruited in Cape Town (e.g., differences in the prevalence of smoking, past contraception, unemployment), but because the number of women in each MOU was relatively small, they were considered as a single group. Overall, there were no significant differences within any center between participants and controls in the demographic characteristics studied, although obviously the characteristics of the cohort of women varied considerably between centers.

Although the choice of main method of contraception at 16 weeks postpartum differed greatly between centers (Table 2), there were no significant differences between participants and controls, with one exception: in Edinburgh, significantly more women who had received antenatal family planning advice had been or were planning to be sterilized (20 women, 11.8%) compared with controls (6 women, 2.8%), $p < 0.01$.

When asked about contraceptive advice received, 90–100% of participants in Edinburgh and Shanghai could recall receiving advice during the antenatal period, compared with only 12% and 13% of controls, respectively (Table 3). In Edinburgh and Shanghai, 67% and 90%, respectively, of the participants said they found the opportu-

Table 2
Mode of delivery and method of contraception being used at 16 weeks; figures are shown as number (%)

| | Edinburgh | | Shanghai | | Cape Town | |
|---|---|---|---|---|---|---|
| | Participants | Controls | Participants | Controls | Participants | Controls |
| Questionnaire returned | 171 (67) | 214 (62) | 254 (98) | 263 (99) | 192 (75) | 197 (78) |
| Delivery | | | | | | |
| Normal | 117 (68) | 139 (65) | 116 (46) | 133 (50) | 170 (89) | 166 (84) |
| Forceps/Ventouse | 22 (13) | 37 (18) | 19 (7) | 17 (7) | 5 (3) | 7 (4) |
| Caesarean | 32 (19) | 38 (18) | 119 (47) | 113 (43) | 17 (9) | 24 (12) |
| Current contraception | | | | | | |
| Oral | 60 (35) | 78 (36) | 3 (1) | 1 (0.4) | 18 (9) | 16 (8) |
| Condom | 72 (42) | 99 (46) | 112 (44) | 114 (43) | 0 | 0 |
| Injectable | 8 (5) | 4 (2) | 0 | 0 | 158 (83) | 155 (79) |
| IUD | 5 (3) | 5 (2) | 7 (3) | 8 (3) | 0 | 0 |
| NFP/Withdrawal | 2 (1) | 3 (1) | 9 (3.5) | 7 (2.7) | 0 | 0 |
| Other | 1 (1) | 4 (2) | 4 (1.5) | 8 (3) | 0 | 0 |
| Nothing/No plan | 3 (2) | 3 (1) | 76 (30) | 70 (26) | 2 (1) | 4 (2) |
| Nothing/No info | 10 (6) | 12 (6) | 0 | 0 | 5 (3) | 9 (5) |
| Nothing/planning pregnancy | 0 | 1 (0) | 0 | 0 | 0 | 0 |
| Breast feeding | 0 | 3 (1) | 39 (15) | 52 (20) | 0 | 0 |
| Sterilisation | 6 (3) | 1 (0) | 0 | 0 | 8 (4) | 13 (7) |
| Combination | 3 (2) | 2 (1) | 4 (2) | 2 (0.8) | 0 | 0 |
| Fertility treatment | 0 | 1 (0) | 0 | 0 | 0 | 0 |
| Pregnant | 0 | 0 | 0 | 0 | 2 (1) | 4 (2) |

nity to discuss contraception during pregnancy helpful. In Edinburgh 23% of women, and in Shanghai just two individual women, did not find the advice helpful, whereas the remainder of the respondents were unsure. In Cape Town, surprisingly, only 36% of the women in the intervention group could remember receiving advice antenatally, no different than the figure for the control group. Only in Edinburgh did the majority of women receive additional contraceptive advice *after* childbirth, and most of them discussed contraception on at least two more occasions: in hospital and with their general practitioner. In Shanghai few women, and in Cape Town hardly any, discussed contraception once they had had their baby.

The response rate to the questionnaire administered at one year postpartum once again varied between centers but not between participants and controls (Table 4). There were no differences in patterns of contraceptive use between participants and controls in any of the centers. In Shanghai, 21% and 23% of participants and controls, respectively, used "other" methods, which for both groups included natural methods (12%) and natural methods plus condoms (6%). In Edinburgh, the significant difference in women choosing sterilization noted at 16 weeks postpartum had disappeared.

Table 5 shows that 8 participants (6%) and 19 controls (10%) in Edinburgh were pregnant (3 and 9 pregnancies, respectively, were planned) or had been pregnant and either spontaneously aborted (2 participants and 5 controls) or had an abortion (2 participants and 1 control). In Shanghai, 29 participants (12%) and 27 controls (11%) had an unplanned pregnancy during the first year after childbirth, and all had the pregnancy terminated. One of these women had been using an intrauterine device (IUD), the rest were using condoms, natural methods, or no method. In Cape Town, there were three pregnancies in the participant group (2%; two were planned) and seven pregnancies in the control

Table 3
Recall of when advice about contraception was received; figures are shown in number (%)

| | Edinburgh | | Shanghai | | Cape Town | |
|---|---|---|---|---|---|---|
| | Participants | Controls | Participants | Controls | Participants | Controls |
| Time of advice | | | | | | |
| Antenatal | 143 (90) | 27 (12)*** | 254 (100) | 35 (13)*** | 69 (36) | 56 (28) |
| Postnatal (hosp) | 106 (63) | 149 (69) | 17 (7) | 13 (5) | 5 (3) | 18 (9)** |
| Postnatal (home) | 105 (63) | 154 (71) | 63 (25) | 47 (18) | 4 (2) | 4 (2) |
| 6-week check | 33 (19) | 43 (20) | 28 (12) | 28 (11) | 1 (1) | 8 (4) |
| No advice recalled | 1 (1) | 8 (4) | 0 | 160 (61)*** | 116 (62) | 121 (64) |

** $p = 0.006$; *** $p < 0.001$.

Table 4
Patterns of contraceptive use at one year after childbirth; figures are shown in number (%)

| | Edinburgh | | Shanghai | | Cape Town | |
|---|---|---|---|---|---|---|
| | Participants | Controls | Participants | Controls | Participants | Controls |
| Questionnaire returned | 140 (55) | 184 (53) | 246 (95) | 249 (94) | 201 (79) | 192 (76) |
| Using contraception | 116 (83) | 146 (79) | 221 (90) | 216 (87) | 175 (87) | 162 (84) |
| Oral | 48 (37) | 62 (39) | 5 (2) | 6 (2) | 23 (12) | 24 (13) |
| Condom | 43 (33) | 60 (37) | 127 (52) | 100 (40) | 2 (1) | 0 |
| Injectable | 4 (3) | 2 (1) | 0 | 0 | 136 (68) | 124 (65) |
| IUD | 2 (2) | 6 (4) | 38 (15) | 54 (22) | 0 | 0 |
| Other | 6 (5) | 9 (6) | 51 (21) | 55 (23) | 0 | 0 |
| Nothing | 2 (2) | 1 (1) | 25 (10) | 33 (13) | 26 (13) | 30 (16) |
| Planning pregnancy | 13 (10) | 13 (8) | 0 | 0 | 2 | 1 |
| Sterilization | 13 (10) | 7 (4) | 0 | 0 | 13 (7) | 14 (7) |

group (4%; one planned). Two of the women in the control group had a spontaneous abortion. There were no significant differences in the number of pregnancies between the participant and the control groups in any of the centers (95% CI for the difference in pregnancy rates between the participants and controls were: $-10.6\%$ to $+1.7\%$, $-4.7\%$ to $+6.6\%$, and $-6.0\%$ to $+1.2\%$ in Edinburgh, Shanghai, and Cape Town, respectively). Furthermore, there were no significant differences in pregnancy rates between participants and controls when all centers were combined ($\chi^2 = 0.8$). Surprisingly, pregnancy rates at one year did not differ significantly between women who did or did not intend to have more children, either in Edinburgh or Cape Town (not relevant in Shanghai), nor did the counseled participants show a significantly greater tendency than controls to differ in pregnancy rates according to childbearing intention. Contraceptive practice at one year, however, did differ according to childbearing intention in Edinburgh and Cape Town, primarily because all sterilized women belonged to the group not intending to have further children, but again the patterns were similar in the two treatment groups (figures not shown).

There were no differences between participants and controls in the patterns of use over the year after childbirth (Table 6). Neither the number of times contraceptive method was changed during the first year postpartum, nor the number of different methods of contraception recorded on the 12-month contraceptive calendar differed between the two groups. Ten percent of both participants and controls used at least three different methods during the year. When continuation rates of contraception were examined, there were no significant differences between participants and controls. In Edinburgh, approximately 75% of both the participant and control groups who were using the combined oral contraceptive pill at 16 weeks postpartum were still using this method at 1 year (approximately 60% for condom usage in both the participant and control groups). In Cape Town, 76% of participants and 75% of controls continued to use injectable methods at 1 year. In Shanghai, 22% of participants and 21% of controls were using condoms at 16 weeks and continued to do so at 1 year postpartum (for IUD usage, the figures were 1% and 2%, respectively).

## 4. Discussion

Although women in all centers said they found the opportunity to discuss contraception antenatally was useful, it did not make any difference to patterns of contraceptive use postpartum. There was one small exception; in Edinburgh more women in the group receiving antenatal advice were sterilized subsequently by 16 weeks. In Edinburgh, the family planning nurse routinely discussed sterilization with women who stated that they planned no further pregnancies, gave advice about the most appropriate timing of sterilization, and how to arrange it. Sterilization by 16 weeks was facilitated if the decision was made during the antenatal period.

Table 5
Pregnancies during the year of follow-up; figures are shown as number (%)

| | Edinburgh | | Shanghai | | Cape Town | |
|---|---|---|---|---|---|---|
| | Participants | Controls | Participants | Controls | Participants | Controls |
| Total | 8 (6) | 19 (10) | 29 (12) | 27 (11) | 3 (2) | 7 (4) |
| Miscarried | 2 | 5 | 0 | 0 | 0 | 2 |
| Termination of pregnancy (TOP) | 2 | 1 | 29 | 27 | 0 | 0 |
| Continuing | 2 | 12 | 0 | 0 | 2 | 4 |
| Not known | 2 | 1 | 0 | 0 | 1 | 1 |

Table 6
Contraceptive use with time postpartum; figures are shown as %

| | 1 Month | | | | | | 3 Months | | | | | | 6 Months | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | Edinburgh | | Shanghai | | Cape Town | | Edinburgh | | Shanghai | | Cape Town | | Edinburgh | | Shanghai | | Cape Town | |
| | Par* | Con | Par | Con | Par | Con | Par | Con | Par | Con | Par | Con | Par | Con | Par | Con | Par | Con |
| Oral | 10 | 11 | 0 | 0 | 4 | 6 | 37 | 30 | 0 | 0 | 6 | 7 | 37 | 36 | 2 | 0 | 7 | 9 |
| Condom | 20 | 18 | 0 | 0 | 0 | 0 | 31 | 34 | 11 | 8 | 1 | 0 | 37 | 37 | 48 | 44 | 1 | 0 |
| Injectable | 1 | 0 | 0 | 0 | 90 | 85 | 4 | 2 | 0 | 0 | 87 | 84 | 5 | 2 | 0 | 0 | 81 | 75 |
| IUD | 0 | 0 | 0 | 0 | 0 | 0 | 1 | 2 | 0.4 | 1 | 0 | 0 | 2 | 3 | 4 | 8 | 0 | 0 |
| Other | 10 | 11 | 0 | 0 | 0 | 0 | 11 | 12 | 4 | 5 | 0 | 0 | 9 | 13 | 19 | 23 | 0 | 0 |
| Nothing | 3 | 3 | 0 | 0 | 1 | 4 | 4 | 4 | 4 | 4 | 3 | 3 | 3 | 3 | 11 | 15 | 6 | 7 |
| Sterilized | 3 | 1 | 0 | 0 | 3 | 6 | 3 | 1 | 0 | 0 | 3 | 6 | 4 | 1 | 0 | 0 | 5 | 6 |
| Not needed | 52 | 56 | 100 | 100 | 3 | 4 | 11 | 15 | 81 | 82 | 0 | 1 | 2 | 5 | 6 | 10 | 0 | 3 |

* Par = Participants; Con = Controls.

We recognized at the outset of the study that it may be difficult to demonstrate an influence on contraceptive use in Edinburgh where the prevalence is already high (89% of both participants and controls were already using contraception at 16 weeks, and 83% and 80%, respectively, at 1 year). We may have introduced bias into the study design in the Edinburgh center because the participants were given the opportunity to decline the additional contraceptive counseling and, hence, were a self-selected group (however, the number of participants declining advice, 37, was small). It is quite possible, however, that women who were less likely to use contraception (or use it reliably) were also less likely to return their questionnaires, and it is not possible to determine whether the intervention may have had an effect on this subgroup. In a study of the quality of postpartum advice in Edinburgh [2], women who were young, unmarried, and defaulted from their 6-week postnatal check were more likely to become pregnant again in the first year after childbirth. An analysis of 147 women in the Edinburgh center who returned neither the 16-week nor the 1-year questionnaire showed them to be significantly younger ($p < 0.001$) and significantly more likely to live in an area of socioeconomic deprivation ($p < 0.001$) than women who responded to both questionnaires. However, there was no difference in parity at the time of recruitment.

In the People's Republic of China, the "one child policy" has been enforced since 1977. As a part of that policy, contraception promotion is perhaps more effective than in any other country in the world. One-hundred percent of women in the subject group remembered receiving contraceptive advice and yet, surprisingly, over 11% conceived despite knowing that these pregnancies would have to be terminated. Our results illustrate that after childbirth women in Shanghai are using less reliable methods of contraception; at 6 months postpartum, over 40% were using condoms and 20% were using "other" methods, which included natural family planning. This would suggest that either the need to use a reliable method of contraception was not stressed sufficiently by the healthcare providers or, alternatively, the advice given was ignored by the client. In either case, our results indicate that it would be beneficial for the policymakers in Shanghai to re-examine their guidelines in this area.

In Cape Town, a high percentage of women in both the participant (83%) and control (79%) groups were using injectable methods of contraception by 16 weeks (68% and 65% for participant and control groups, respectively, at 1 year), and this is reflected in a smaller number of pregnancies during the year of follow-up in comparison with the other two centers. Paradoxically, at least 62% of women in both groups could not recall receiving contraceptive advice at any time. This could be explained by a misinterpretation of the word "advice," particularly in the Xhosa dialect in Cape Town. Even though the questionnaires were translated and then back-translated independently, the advice given about postpartum contraception may have been considered to be routine and not additional information or regarded as "advice," possibly because of the background level of postpartum contraceptive education given antenatally.

In Edinburgh, oral contraceptive pills and condoms were the main contraceptive methods used at three months with no change at six months postpartum. The use of condoms is perhaps surprisingly high, which may reflect a desire by the client for another pregnancy in the near future. The high continuation rates of injectable methods at both six months and one year in Cape Town illustrate efficient and effective provision of family planning services by MOUs.

Very few studies have examined the effects of antenatal counseling on postpartum contraception. There is some evidence that women are more receptive to advice given antenatally [3] and, indeed, that women may wish to discuss contraception antenatally and also post hospital discharge [4]. A study conducted in Egypt on the impact of antenatal counseling on couples' knowledge and practice of contraception, followed-up immediately after delivery and three months later, found that counseling sessions did improve couples' knowledge and practice in the study group. Furthermore, involving husbands in family planning counseling sessions led to joint decisions being made and encouraged women's use of contraception [5]. In contrast, a study that

investigated the contraceptive choices amongst Nigerian women attending an antenatal clinic concluded that their family planning program should be restructured and redirected to improve services at the community level [6]. A medical bulletin from International Planned Parenthood Federation (IPPF) suggests that postpartum contraception should also be included in the training of traditional birth attendants [7].

There have been many studies published concerning contraceptive counseling during the postnatal period. In Nepal, a trial of one-to-one counseling of mothers immediately after delivery and three months later had no effect on knowledge of child care or infant health, but produced a slight improvement in contraceptive uptake (from 14% to 20%) at six months postpartum [8]. In the UK, it remains a neglected area by obstetricians, as illustrated in a recent review by the Royal College of Obstetricians and Gynaecologists of the puerperium and postnatal care [9], where, it is significant to note, that postnatal contraception was not even mentioned in a review that included topics such as postnatal depression and breast problems. Our study demonstrated that the majority of women in Scotland had contraceptive advice at least once during the postnatal period, usually from a midwife or health visitor.

The recently updated Cochrane report [10] regarding the effectiveness of postpartum education on contraceptive use concluded that this area has not been evaluated adequately. The report stated that postpartum education may be effective in increasing the short-term use of contraception; however, there was limited data on the longer term effect on the prevention of unplanned pregnancies and also a lack of randomized controlled trials. The report called for research to assess "the effectiveness of the minimalist education provided in more developed countries and the variety of programs provided in less developed regions." Indeed, the very basis on which most postpartum education programs are devised has been questioned [11]—that postpartum women are motivated to use contraception and that they will not return to a health center for family planning advice. Postpartum contraceptive advice should perhaps be modeled on a study by Huezo and Malhotra [12], based on family planning clinics in Guatemala, Trinidad, Tobago, Hong Kong, Jordan, Nepal, and Kenya, where an attempt was made to look at the various factors that may affect clients' choice of a contraceptive method and to identify factors which may affect either the duration of use of the chosen method or the clinic services. It was found that a high counseling score did not have a beneficial effect on use continuation. The authors suggested that very often, because too much time is spent on issues that are not essential or relevant to the client, the person providing counseling has to rush when providing instructions to clients on the proper and consistent use of the chosen contraceptive method or in responding to the questions raised by the client.

Studies such as the one described in this article involving operations research are difficult to perform and monitor. As the confidence limits demonstrate, in our study we could be failing to detect a true effect on the pregnancy rate of up to 5–10% in each center even with our large sample sizes, so we cannot conclude that the antenatal advice given was totally ineffective. It is possible that although participants received individualized counseling from a trained family planning nurse antenatally, the content of the counseling was not sufficiently different from the standard care to enhance effective contraceptive use. Perhaps if other centers had been chosen, centers where the use of postpartum contraception is less prevalent, contraceptive advice given during the antenatal period may have had a demonstrable effect. On the other hand, it is possible that so many other factors affect contraceptive use that dedicating resources to any more elaborate (and expensive) programs than the ones that already exist may be a waste of money and effort.

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# Dewhurst's Textbook of Obstetrics and Gynaecology for Postgraduates

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# Chapter 31: Contraception

A. Glasier

In the UK over 90% of couples wishing to avoid pregnancy use a method of contraception. A recent survey of sexual attitudes and lifestyles (Johnson *et al.* 1994) showed the combined oral contraceptive (COC) pill is the most commonly used method of contraception with condoms a close second (Table 31.1).

No method of contraception is completely effective and failure rates for most reversible methods are strongly influenced by compliance. Pregnancy rates measured in clinical trials are often lower than those experienced in day-to-day use, since they are more likely to reflect perfect or near perfect use. The comparative efficacy of all methods currently available in the UK is shown in Table 31.2. By convention failure rates are expressed as

**Table 31.1** Contraception used in the UK in 1994. After Johnson *et al.* (1994)

| | % |
|---|---|
| Oral contraception | 28.8 |
| Condom | 25.9 |
| Vasectomy | 12.6 |
| Female sterilization | 11.0 |
| IUD | 6.6 |
| Withdrawal | 4.2 |
| Diaphragm | 2.3 |
| Rhythm | 1.9 |
| Spermicides | 1.1 |
| Abstinence | 1.0 |
| Other | 0.7 |

**Table 31.2** Failure rates of contraception

| Method | Method failure (per 100 women-years) | User failure (per 100 women-years) | Cumulative pregnancy rate (%) |
|---|---|---|---|
| Combined pill | 0.1 | 2.8 | |
| POP (25–29 years) | 3 | 10 | |
| (> 40 years) [1] | 0.3 | | |
| DMPA | 0.1 | | |
| Norplant | 0.5 | | 1.0 at 3 years<br>2.7 at 5 years |
| Copper IUD | | | |
| < 200 m² | 2.8 | | |
| > 200 m² | 0.7 | | 3.2 at 8 years |
| LNG-IUS | 0.1 | | 0.4 at 5 years |
| Female sterilization | 0.13 | | 1.8 at 10 years |
| Male sterilization | 0.01 | | 0.1 at 10 years |
| Diaphragm | 4–8 | 10–18 | |
| Male condom | 4–8 | 10–18 | |
| Female condom | 4–8 | 10–25 | |
| Rhythm | | 20–40 | |
| Mucus method | 1–5 | 17–22 | |
| $PC_4$ | 20–26% failure rate | | |

the number of pregnancies each year among 100 women using the method (100 women-years). For long-acting methods the cumulative pregnancy rate over a period of time is often more helpful.

## COC pill

The COC pill contains both oestrogen — usually ethinyl oestradiol — and a progestogen. The dose of oestrogen varies from 20 to 50 μg, most women now using the so-called 'low dose pills' containing 30–35 μg. Low dose pills are potentially safer since the cardiovascular risks of the pill are mainly due to oestrogen. Although the lowest dose pills currently available (20 μg ethinyl oestradiol) have the same efficacy as 30 μg pills, cycle control is less effective and breakthrough bleeding more common. The progestogens used in currently available pills fall broadly into three groups, first- and second-generation progestins (e.g. norethindrone and levonorgestrel, respectively) and the third-generation series including gestodene, desogestrel and norgestimate. The pill is taken for 21 days followed by a 7-day break (the pill-free interval or PFI) during which time withdrawal bleeding usually occurs.

Combined pills are available as monophasic preparations, in which every pill in the packet contains the same dose of steroids, and biphasic and triphasic preparations in which the dose of both steroids changes once or twice during the cycle. Phasic pills were introduced in order to reduce the total dose of progestogens and in the belief that a regimen which mimicked the normal cycle would produce better cycle control. There is no evidence for better cycle control; failure rates may be higher if woman get confused about how to cope with missed pills. Every day (ED) preparations in which a placebo tablet is taken during the PFI may improve compliance.

### Mode of action

The principal mode of action of the combined pill is the inhibition of ovulation. Oestrogen inhibits pituitary follicle-stimulating hormone (FSH), suppressing the development of ovarian follicles, while progestogens inhibit the development of the luteinizing hormone (LH) surge. In some women, the 7-day PFI is long enough to allow early follicular growth and 25% have ultrasound evidence of follicles 10 mm in diameter on the last day of the PFI. If the PFI is extended beyond 7 days these follicles will continue to develop and, despite restarting the pill, ovulation may occur. For women who appear to have conceived as a result of a genuine pill failure and who wish to continue using the COC the PFI can be shortened to 4 days to ensure suppression of follicular development.

Additional contraceptive effects include changes in cervical mucus characteristics interfering with sperm transport: a possible alteration in tubal motility; endometrial atrophy; and impaired uterine receptivity.

### Efficacy

See Table 31.2.

### Advantages of the combined pill

The COC confers a number of health benefits. Menstrual periods are usually lighter, shorter and more regular during pill use. They also tend to be less painful and premenstrual symptoms less troublesome. For women without contraindications to oestrogen the combined pill is often the first choice of treatment for dysmenorrhoea, premenstrual syndrome, menorrhagia and anovulatory dysfunctional uterine bleeding. In countries where iron deficiency anaemia is common, COC use reduces the incidence through decreased menstrual blood loss.

Other benefits include a decreased incidence of benign breast lumps, functional ovarian cysts, endometriosis, acne and possibly pelvic inflammatory disease. There is substantial evidence that COC use protects against ovarian and endometrial cancer. In a review of the published literature the World Health Organization (WHO 1992) concluded that there is a 50% reduction in the risk of epithelial ovarian cancer after 5 years use of the COC. The protective effect persists for at least 10 years after pill use stops. The mechanism for the protective effect is unclear but may be related to the reduction in the total number of ovulations, and therefore rupture of the ovarian capsule, experienced in a lifetime.

In the same WHO meta-analysis COC use was similarly shown to reduce the risk of endometrial cancer with an effect strongly related to the duration of use. The risk is reduced by 20% after 1 year and by about 50% after 4 years. The protective effect seems to be sustained for perhaps as long as 15 years after stopping the pill.

### Contraindications

The absolute contraindications to the COC are listed in Table 31.3.

Relative contraindications include the presence of serious, or multiple, risk factors for arterial disease — family history; diabetes mellitus; smoking; increasing age; obesity; and migraine. Hyperprolactinaemia is also a contraindication since oestrogen stimulates the lactotrophes increasing prolactin concentration.

Table 31.3 Absolute contraindications to the COC pill

| |
|---|
| Ischaemic heart disease including cardiomyopathy |
| Most types of valvular heart disease |
| Arterial thrombosis |
| Venous thrombosis or known predisposition to thrombosis |
| Past cerebral haemorrhage and current transient ischaemic attacks |
| Vascular malformations of the brain |
| Pulmonary hypertension |
| Hyperlipidaemia |
| Focal and crescendo migraine and migraine requiring ergotamine treatment |
| Active liver disease, recurrent cholestatic jaundice and Dubin–Johnson or Rotor syndrome |
| Liver tumour |
| Known gallstones |
| Porphyria |
| History of serious condition known to be affected by steroids, e.g. trophoblastic disease |
| Pregnancy |
| Undiagnosed genital tract bleeding |
| Oestrogen-dependent neoplasms, e.g. breast cancer |

## Risks and side-effects

### MINOR SIDE-EFFECTS

The recent publication of the 25 year follow-up of woman using the COC (Beral *et al.* 1999) concluded that ten years or more after COC use ceases mortality is similar among pilot users and that of newer users

Contraceptive steroids are metabolized by the liver and affect the metabolism of carbohydrates, lipids, plasma proteins, amino acids, vitamins and clotting factors. The combined pill has an effect on almost every system in the body. Most side-effects are minor and include weight gain, fluid retention, headache, nausea and vomiting, chloasma, mood change, loss of libido, mastalgia, breast enlargement and greasy skin. Many improve within 3–6 months of starting the pill but side-effects often lead to discontinuation. It is worth trying a different dose of oestrogen or type of progestogen if time alone does not solve the problem.

### SERIOUS SIDE-EFFECTS

Serious side-effects involve mainly the cardiovascular system and the pill affects both the venous and arterial circulation. In both cases the increased risk appears to be related to an increased thrombotic tendency. Alterations in clotting factors create a tendency to hypercoagulability which is partly balanced by an increase in fibrinolysis. The adverse effect on clotting is related to the dose of oestrogen and lower dose pills are associated with a reduced risk compared with pills containing 50 μg of oestrogen.

*Venous disease*

Women who take the combined pill have an increased risk of venous thromboembolism (VTE) compared with non-users — the relative risk is 4.5 among European women. The risk is unaffected by age, smoking or duration of pill use but is higher in obese women (body mass index > 25 kg/m$^2$) and possibly among women with a history of pregnancy-induced hypertension (PIH). Four studies published in 1995 and 1996 (McPherson 1996) demonstrated a differential risk of VTE depending on the type of progestogen in the pill. Combined pills containing either gestodene or desogestrel were shown to have a roughly twofold increased risk of VTE when compared with first- or second-generation combined pills. The effect may result from the balance between oestrogens and the newer less androgenic progestins which antagonize oestrogens less. (There may alternatively or additionally be a direct effect of progestins on clotting mechanisms although there is no good evidence for this.)

The publication of these studies led to widespread publicity and in the UK, Germany and Norway restrictions were placed on the use of pills containing gestodene or desogestrel. These restrictions were removed in the UK in 1999 but woman should be informed about the different risks associated with pills containing third generation progestins.

The risk of venous thrombosis returns to normal by 3 months after stopping the pill.

*Arterial disease*

Arterial disease among pill users is much less common but more serious. It is related to age and the risk is strongly influenced by smoking.

1 Women who do not smoke, have hypertension or diabetes are at no increased risk of myocardial infarction if they use the COC, regardless of age. The risk is increased by hypertension (×3) and by smoking (×10) (WHO 1998). The risk of myocardial infarction was thought theoretically to be reduced among users of third-generation progestin-containing pills since these are associated with more cardioprotective lipid profiles (increased concentrations of high density lipoproteins in particular) and may also have an increased tendency to fibrinolysis. These effects too are probably related to the less androgenic and effectively more oestrogenic nature of the pills. Although preliminary epidemiological data have suggested a reduction in the incidence of myocardial infarction among users of third- compared with second-generation pills, the difference is not statistically different.

2 In woman who do not smoke or have hypertension, the risk of ischaemic stroke is increased by 1.5 fold among

current users of the COC. The risk of haemorrhagic stroke is not increased. Smoking and hypertension significantly increase the risks of both types of stroke. The incidence of haemorrhagic stroke increases with age and current use of the COC may magnify this effect.

In the RCGP study (Beral *et al.* 1999) the relative risk of dying from cerebrovascular disease was 1.9 among current and recent users (within ten years) compared with newer users.

3 Most women have a small but non-significant rise in both systolic and diastolic blood pressure when they start the pill. Approximately 1–3% become clinically hypertensive and the incidence increases with age. PIH does not predispose to hypertension during pill use.

4 The COC is also contraindicated in migraine which is or may be associated with transient cerebral ischaemia. This includes crescendo migraine and focal migraine with asymmetric symptoms. Symmetrical blurring of vision, generalized flashing lights or photophobia associated with unilateral headache are not features which are regarded as absolute contraindications. It is important therefore to take a detailed history before refusing to prescribe the COC for someone with a history of 'migraine'.

*Malignant disease*

*Breast cancer*. Published data on the pill and breast cancer are difficult to interpret because pill formulations and patterns of reproduction (particularly age at first pregnancy) have changed with time. WHO (1992) concluded that while there appears to be no overall association between oral contraceptive use and the risk of breast cancer there is a weak association between pill use and breast cancer diagnosed before the age of 36 years and possibly up to the age of 45 years. In 1996 the Collaborative Group on Hormonal Factors in Breast Cancer (1996) reported a meta-analysis of 54 studies involving over 53 000 women with breast cancer and 100 000 control subjects. The meta-analysis is thought to include 90% of the published data. The group concluded that use of the COC was associated with a small increase in breast cancer and that the increased risk persisted for 10 years after stopping the pill. The relative risk for current users was 1.24, for 1–4 years after stopping 1.16 and for 5–9 years after stopping 1.07. After 10 years the relative risk was the same as that of non-users. Although the relative risk was higher for women who started the pill at a young age (because breast cancer is rare in this age group) there was little added effect from the duration of use, dose or type of hormone. Ever-users were significantly less likely (relative risk 0.88) to have metastatic disease even if they had stopped the pill more than 10 years earlier. It has been suggested that starting to use the pill may accelerate the appearance of breast cancer in susceptible women. Alternatively, women using the pill might have their tumours diagnosed earlier although it is difficult to explain why a tendency to earlier diagnosis would persist for years after stopping. A biological effect of combined hormonal contraception is still a possibility.

*Cervical cancer*. Data on the risk of cervical cancer among pill users is also difficult to interpret since barrier methods confer some protection and cervical cancer is often regarded as a sexually transmitted disease. More than 5 years of pill use may be associated with a small increase in the risk of squamous carcinoma of the cervix but pill users are a captive population for cervical screening. Recent evidence has suggested an increased risk of adenocarcinoma among long-term users but this is a rare tumour. In the RCGP study (Beral *et al.* 1999) the relative risks of dying from cervical cancer was 2.5 among current and recent (within 10 years) users.

*Liver cancer*. Benign hepatic adenoma is a rare consequence of COC use.

PRACTICAL PRESCRIBING

Women should be carefully instructed how to use the pill and what to do when pills are forgotten (Fig. 31.1). Woman with a strong FH of VTE may be scanned for inherited thrombophilia. Many women choose or are advised to have a break from using the pill for a few months. While most cardiovascular risks decline when the pill is stopped they recur as soon as it is started again and unplanned pregnancies commonly occur during such breaks. Most women who stop the pill regain normal fertility within 3 months. Secondary, so-called postpill amenorrhoea is almost always the result of abnormalities present before the pill was started (such as polycystic ovarian syndrome) but regular COC-induced withdrawal bleeds mask these conditions. There is no evidence of any adverse effect on the fetus as a result of previous pill use, and there are no teratogenic effects reported.

## Progestogen only contraception

Progestogen only contraception was introduced to avoid the side-effects of oestrogen. Although much less commonly used than combined hormonal contraception it is available in a wide variety of systems including oral, implants, long-acting injectables and more recently hormone-releasing intrauterine devices (IUDs).

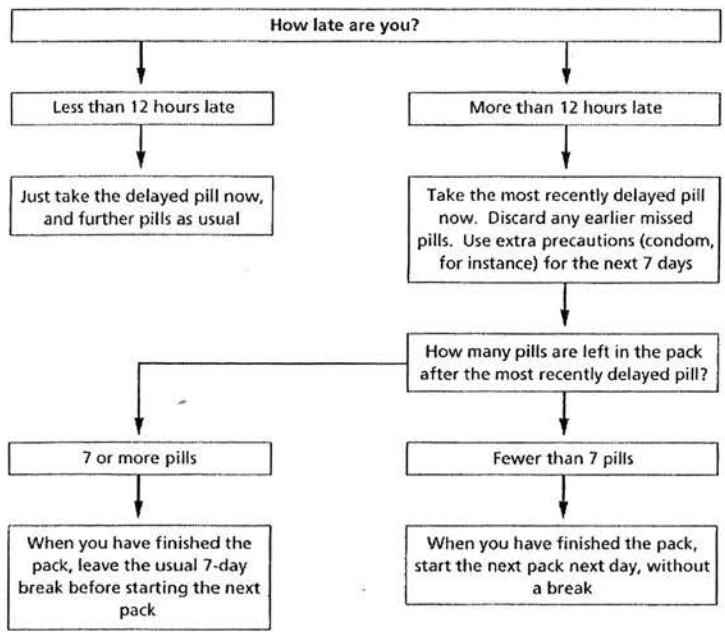


Fig. 31.1 Instructions for missed pills. What to do if the patient has forgotten to take pills at the right time.

#### MECHANISM OF ACTION

All methods have a number of mechanisms of action. Given in high doses, e.g. injectables, progestogens inhibit ovulation. In low doses ovulation may be inhibited, often inconsistently, depending on the individual response. By all routes of administration progestogens affect cervical mucus reducing sperm penetrability and transport and all have an effect on the endometrium which probably compromises implantation.

#### SIDE-EFFECTS

All low dose progestogen only methods are associated with a high incidence of irregular vaginal bleeding. This is due in part to their effect on ovarian function. In the normal cycle ovulation determines regularity. Inconsistent ovulation and fluctuating endogenous oestrogen production from irregular follicle growth leads to irregular bleeding. There is evidence to suggest that progestogen only methods also alter the vasculature of the endometrium increasing the chance of bleeding.

#### ORAL PROGESTOGEN-ONLY METHODS

A number of different progestogens are available although as yet there are no preparations marketed containing the third-generation progestogens. The progestogen-only or mini-pill (POP) is available in daily doses of between 30 and 75 μg and these lead to peak concentrations of around 2.5 nmol/l. It is important to understand that not only do these pills not contain oestrogen but the dose of progestogen is often considerably lower than that delivered by the combined pill. A 28-day course of Microval, for example, exposes the user to a total dose of 0.84 mg of levonorgestrel compared to 3.15 mg during 21 days use of Microgynon or 5.25 mg of Ovranette. Thus the mini-pill is suitable for women with conditions on which the effect of progestogens on lipids may be detrimental, e.g. mild hypertension.

Around 50% of women using the POP continue to ovulate normally and regularly, 10% will experience complete suppression of ovulation while the rest will have inconsistent ovulation often with a short luteal phase or follicular development only. The last group will experience irregular bleeding and up to 20% of users discontinue the POP for this reason.

##### *Efficacy*

The POP has a higher failure rate than the combined pill although the difference is less marked in women over the

Table 31.4 Contraindications to progestogen-only contraception

*Absolute*
Known or suspected pregnancy – high dose androgenic progestogens such as NET-EN may carry a very small risk of masculinization of a female fetus
Undiagnosed irregular vaginal bleeding
Any serious side-effect which is not clearly oestrogen-related
Current history of serious cardiovascular disease
Injectable methods should not be used by women with a bleeding tendency – including long-term anticoagulation – because of risk of injection-site haematoma

*Relative*
Severe obesity – the efficacy of low dose methods may be reduced and injectable may exacerbate weight gain
Breast cancer
Molar pregnancy until urine is free of human chorionic gonadotrophin
Severe hypertension
History of recurrent ovarian cysts – this does not apply to injectable methods
Chronic liver conditions

age of 30 years (see Table 31.2). The reduced efficacy is due in part to the fact that many women continue to ovulate and in part because the POP has a shorter half-life in the circulation so that missing even just one pill may interfere with contraceptive efficacy.

*Indications and contraindications*

The POP is commonly prescribed for women in whom oestrogen is absolutely or relatively contraindicated, e.g. women with cardiovascular risk factors, migraine, diabetes or mild hypertension. It used to be taught that because of the increasing endogenous risk of arterial disease (myocardial infarction and cerebrovascular accident) with age, women over the age of 35 years should stop using the combined pill and switch to the POP. This is no longer regarded as necessary except for women with risk factors for arterial disease such as smoking, obesity or family history. The other large group of POP users is lactating women since oestrogen impairs milk production. Contraindications which apply to all progestogen only methods are shown in Table 31.4. In many countries regulatory authorities still insist on a long list of contraindications which really only apply to the combined pill.

*Side-effects*

As discussed the commonest cause for discontinuation is irregular bleeding. The effect of the POP on ovarian activity also results in a relatively high incidence of functional ovarian cysts or, more accurately and in many cases, persistent follicles. It has been estimated that 1 in 5 women using the POP will have a 'cyst' demonstrable by ultrasound. Usually these are asymptomatic but can cause abdominal pain or dyspareunia. Most will disappear with menstruation and so treatment should be conservative.

Other side-effects include headache, nausea, bloating, breast tenderness and mood change. These often settle with time but if not, may be alleviated by changing to a different progestogen. Oily skin and acne can be a problem with the more androgenic progestogens – levonorgestrel and norethisterone. Some studies suggested an increased risk of ectopic pregnancy. This has not been confirmed although it is probably true that the POP protects much more effectively against intrauterine than ectopic pregnancies.

*Long-term risks*

Because progestogen only methods are much less prevalent than the combined pill, data on long-term risks are sparse. Depo Provera confers a high degree of protection against endometrial carcinoma but although it should theoretically also protect against ovarian cancer there are as yet no data to support this. There are no data on risks of cervical cancer although it is thought that all hormonal contraception may play a very small promoting role. The recent meta-analysis on breast cancer and hormonal contraception (Collaborative Group on Hormonal Factors in Breast Cancer 1996) included a small percentage of POP (0.8%) and injectable (1.5%) users. Use of the POP within the last 5 years was associated with a very small but statistically significant increase in relative risk of breast cancer (1.17%). The same increase among injectable users was not, however, significant. For both methods the relative risk had returned to normal 5 years after stopping.

## INJECTABLE PROGESTOGEN ONLY METHODS

Long-acting injections of norethisterone–enanthate (NET-EN) and medroxyprogesterone acetate (DMPA) have been available for many years. Although equally effective NET-EN is little used in the UK as the preparation has to be warmed before it can be drawn-up and must be given every 8 weeks (at least initially) as compared with 12 weeks for DMPA (Depo Provera).

Depo Provera is given by intramuscular injection, 150 mg every 12 weeks. The high dose inhibits ovulation and by the end of 1 year of use 80% of women have very infrequent scanty vaginal bleeding or amenorrhoea. Heavy prolonged bleeding may be a problem in around 2% of women, it may be temporarily controlled by the adminis-

tration of oestrogens (simply by adding the combined pill), but will sometimes necessitate discontinuation.

*Side-effects*

It may take up to 1 year for normal fertility to return following cessation of Depo Provera and women who experience bleeding problems while using the method will often continue to do so for months after stopping. This delay in fertility makes Depo Provera an inappropriate method for women wishing short-term contraception. Other side-effects include weight gain and a reduction in bone mineral density (BMD). Data on the latter are few and bone loss appears to be reversible. Amenorrhoea with prolonged use of Depo Provera is associated with hypo-oestrogenism. It has been suggested that BMD may be protected by the addition of oestrogen (e.g. hormone replacement therapy patch) but there are as yet no data to support this and moreover many women who use DMPA have contraindications to oestrogen. It also adds considerably to the cost of the method. In the absence of data it may be sensible to measure BMD in women aged 45 years and over who have been using the method long term and to stop treatment if density is reduced, allowing recovery before the natural menopause.

### PROGESTOGEN ONLY IMPLANTS

Norplant® is a long-acting hormonal method of contraception consisting of six flexible capsules releasing a low dose of levonorgestrel (30–35 μg/24 h after 18 months). The capsules are inserted subdermally in the inner aspect of the upper arm under local anaesthesia. Insertion and removal are minor surgical procedures which require specialized training.

Norplant® is highly effective (see Table 31.2). It lasts for 5 years and fertility returns rapidly after removal.

As with all low dose progestogen only methods menstrual disturbance is the most frequently reported side-effect, and occurs in nearly all users. Norplant® is expensive even if used for 5 years but the additional cost is justifiable as the lack of need for compliance guarantees low failure rates. However, long-term use is essential for cost effectiveness, and careful counselling, particularly about menstrual irregularities, is vital to avoid premature discontinuation.

Variable discontinuation rates have been reported from different countries. In the UK continuation rates of around 85% at 1 year and 72% after 2 years have been reported. Menstrual change accounts for more than 50% of discontinuations.

From the Autumn of 1999, Norplant® will ceased to be manufactured in the UK. Its place will almost certainly be taken by Implanon®, a single implant containing 68 mg etonorgestrel and releasing about 67 μ/day over three years. A disposable inserted, facilitates insertion and, of course removal of one rod is much easier than removing six. Efficacy and side-effects are similar to Norplant® and Implanon® will be available in late 1999.

## IUD

IUDs have been used throughout the world for more than three decades. The Lippes loop and Margulies spiral — made of biologically inert polyethylene — appeared in the early 1960s. The addition of copper to the device improved efficacy enabling the development of smaller IUDs with fewer side-effects, particularly menorrhagia and dysmenorrhoea. These early copper IUDs — the Cu 7 and T Cu 200 — were superseded by a second generation of longer lasting, more effective devices including the Multiload, Nova T and T Cu 380A which is now regarded as the 'gold standard' against which other IUDs are evaluated. These devices contain either more copper wire than their predecessors, copper sleeves and/or a copper wire with a silver core.

Hormone-releasing IUDs were developed in the 1970s but it was not until 1995 that a levonorgestrel-releasing device (Mirena) became available in the UK. Marketed as an intrauterine system (LNG-IUS) to distinguish it from non-medicated devices, the LNG-IUS has a sleeve of levonorgestrel 52 mg around its stem, releasing 20 μg of levonorgestrel per day and lasting for at least 5 years.

New developments aim to reduce side-effects and expulsion. A smaller, lighter T-shaped copper IUD — the CU-SAFE 300 which is designed for insertion without a plunger — moves towards the fundus when the uterus contracts. A frameless IUD, the Flexigard, Gynaefix or Cufix consists of six small copper beads threaded onto a surgical nylon thread the top of which is knotted and embedded to a depth of 1 cm in the uterine fundus. A T-shaped copper device with the tip of each arm expanded into a soft ball is designed to block the ostia to the fallopian tubes.

Tailess or threadless IUDs may reduce the incidence of infection. Many have been tried. Preliminary trials of the Butterfly IUD, designed to be removed with an IUD hook, are promising.

### EFFICACY

The currently available copper IUDs are similar in terms of effectiveness (see Table 31.2), side-effects, expulsions and continuation rates. The LNG-IUS is more effective.

## MECHANISM OF ACTION

It had been believed that the IUD worked by preventing implantation. For many users this mode of action is morally unacceptable and much effort has been invested in attempting to demonstrate that the IUD works at an earlier stage in the cycle. IUDs stimulate a marked inflammatory reaction in the uterus. The concentration of macrophages and leucocytes, prostaglandins and various enzymes in both uterine and tubal fluid increase significantly. It is thought that these effects are toxic to both sperm and egg and interfere with sperm transport. The effects on the endometrium will almost certainly prevent implantation should a healthy fertilized egg reach the uterine cavity.

## SIDE-EFFECTS

### *Menstrual disturbance*

The effects of the IUD on the endometrium — particularly the effect on local prostaglandins — tends to cause increased menstrual bleeding and dysmenorrhoea. In clinical trials up to 15% of women will discontinue for these reasons. Bleeding can be both heavier and more prolonged. In contrast the levonorgestrel-releasing IUS decreases blood flow. Although the 20 μg dose of levonorgestrel is small it causes endometrial atrophy. Andersson and Rybo (1990) demonstrated that after 1 year of use median blood loss fell to 10 ml among 19 women with menorrhagia.

### *Perforation*

Perforation of the uterus may occur at the time of insertion although it is often unnoticed. In large clinical trials it occurs in 1.3 of every 1000 insertions. Routine follow-up 6 weeks after insertion allows most perforations to be detected. Absent threads should be investigated by ultrasound. At this stage the IUD can often be retrieved laparoscopically; left for months local adhesion formation often necessitates laparotomy. There has been widespread debate over the routine use of a tenaculum during IUD insertion. On balance the consensus is that a tenaculum should be used in order to reduce the risk of perforation.

### *Expulsion*

Reported expulsion rates vary from less than 1 to over 7 per 100 women in the first years of use. Expulsion is most common in the first 3 months of use. Many clinicians advise that IUD users should regularly check to feel the IUD strings in order to detect expulsion. In reality this is often not easy to do and results in more anxiety than it prevents unrecognized expulsion.

### *Ectopic pregnancy*

Women using an IUD face an 80% reduction in the risk of ectopic pregnancy compared with women not using contraception; with the LNG-IUS the reduction is 90%. IUDs, however, give less protection against ectopic pregnancy than either hormonal contraception or barrier methods. Some 3–20% of pregnancies which occur during IUD use are ectopic. Since failure is uncommon, the overall risk of ectopic pregnancy is less than 1.5 per 1000 women-years of IUD use.

### *Pelvic infection*

The risk of pelvic infection associated with IUD use has been overestimated. A WHO meta-analysis (Farley *et al.* 1992) suggested that the risk had halved during the 1980s. Infection is most likely to occur during the 20 days following insertion. Thereafter, the risk of developing infection is not significantly higher than that among women using no contraception (< 1.5 per 1000 women-years).

The risk can be reduced by using aseptic techniques during insertion and by restricting the method to women who do not have multiple partners and whose partners do not have multiple partners. Marital status and parity are really irrelevant (in the late 20th Century) to the risk of pelvic inflammatory disease. In some areas where the prevalence of sexually transmitted diseases is high, bacteriological and *Chlamydia* screening are recommended prior to insertion. The risk of infection varies with the type of IUD. The Dalkon Shield (now unavailable) carried the highest risk and is still the subject of litigation in the USA despite the overwhelming evidence that IUD use is not associated with infertility. The LNG-IUS is thought to have a reduced risk of infection, presumably resulting from the effect of levonorgestrel on cervical mucus reducing the risk of ascending infection.

## INSERTION AND REMOVAL

For women who are using effective contraception an IUD can be inserted at any time in the cycle. Otherwise insertion should be limited to the first 7 days of the cycle when, in any case, natural cervical dilatation may reduce discomfort. Postpartum insertion should be delayed until 8 weeks when the risk of expulsion is lower and, in women who are lactating, the risk of perforation will have returned to normal. An IUD can be inserted immediately after spontaneous or therapeutic abortion although expulsion rates may be higher in second trimester abortions.

IUDs specifically designed for immediate postpartum insertion are now available.

Unless pregnancy is desired removal should only be undertaken in the late luteal phase of the cycle or in the first 7 days. In menopausal women the IUD should be left in for 1 year after the last menstrual period. If the IUD threads are not visible or snap during removal it may be possible to remove the device with a specially designed hook or a pair of artery forceps.

Pelvic actinomycosis can rarely occur in association with IUD use. Actinomycosis-like organisms (ALOs) are sometimes seen on smears but if the women is symptom-free the IUD can be left and the smear repeated 6–12 months later. If there are symptoms the IUD should be removed avoiding contamination from the vagina and, after cutting off the tails which will be contaminated, sent for culture.

## Emergency contraception

Emergency contraception is defined as any drug or device used after intercourse to prevent pregnancy. It has been suggested that millions of unwanted pregnancies could be prevented if emergency contraceptives were widely used (Trussel *et al.* 1996).

### COMBINED OESTROGEN AND PROGESTOGENS

The hormonal regimen most widely used for emergency contraception is a combination of 100 µg ethinyloestradiol and 0.5 mg levonorgestrel taken twice with the two doses separated by 12 h (the CEP regimen). A licensed product ($PC_4$) is available in the UK; however, the same hormones are available in some brands of COC and these are often used because they are considerably cheaper. Whether combined pills containing other progestogens are effective when administered in the same manner is not known but seems likely.

#### *Mechanism of action*

The mode of action of CEP remains unclear but it probably works by either inhibiting, or in some way compromising, ovulation. It has also been suggested that the CEP regimen may cause luteolysis or interfere with implantation but there is no good evidence for this and hormonal emergency contraception may be less effective after ovulation.

#### *Efficacy*

Accurate estimates of efficacy are difficult to make (see Table 31.2). Many women are unsure of the exact date of their last menstrual period and most do not ovulate on exactly the same day each cycle. The majority of women who use emergency contraception are of unproven fertility and many use it after an accident with a condom which may not in fact have resulted in the leakage of seminal fluid. The chance of conception following one act of intercourse has been calculated to be around 27% per cycle so that even without emergency contraception over 70% of women will not conceive.

#### *Side-effects*

Nausea (up to 50%) and vomiting (up to 20%) are the main side-effects of the CEP regimen. Subsequent menses normally occurs at the expected time but may be heavier than usual, and some women experience mastalgia. Although the method is only used within 72 h of intercourse no one knows whether it is effective beyond this time limit.

Theoretically use of the CEP regimen once every month exposes a woman to less risk from contraceptive steroids than if she were to use the COC pill — although it exposes her to a greater risk of pregnancy.

Few data are available on the safety of the CEP regimen, but recently both the WHO and the International Medical Advisory Panel of the International Planned Parenthood Federation have advised that there are no absolute contraindications to its use. There is no evidence that the CEP regime is teratogenic should it fail to prevent pregnancy.

High dose oestrogens and progestogen alone are also effective when given postcoitally.

### LEVONORGESTEREL ALONE

Levonorgesterel 0.75 mg taken twice with two doses separated by 12 hours may be more effective than the CEP regimen and is certainly better tolerated (WHO 1999). Both levonorgesteral and CEP may well be more effective if they are taken as soon after intercourse as possible. This method is likely to become available in the UK in 1999.

### IUD

The IUD is a highly effective postcoital contraceptive with failure rates of less than 1%. In the UK it is used forup to 5 days after the estimated day of ovulation, which may be more than 5 days after intercourse. It is particularly appropriate for women who wish to continue the IUD as a long-term method of contraception. Most women requesting emergency contraception are, however, young and nulliparous and it can sometimes be difficult to insert a device.

Health economists in the UK have estimated that every pregnancy prevented by the use of hormonal emergency

contraception saves the National Health Service (ignoring the cost to society of bringing up a child) at least £500.

## Sterilization

In Britain almost 50% of couples aged 35–44 years are using either male or female sterilization as their method of contraception. Vasectomy is safer, cheaper and performed under local anaesthesia and the ability to check for efficacy is a clear advantage when male is compared with female sterilization. Male fertility, however, continues well beyond that of women and these differences should be discussed during counselling.

### FEMALE STERILIZATION

Female sterilization usually involves blocking both fallopian tubes by laparotomy, mini-laparotomy, or more commonly by laparoscopy. Bilateral salpingectomy or hysterectomy may be preferable when there is coexistent gynaecological pathology. Mini-laparotomy and laparoscopic sterilization are probably equally safe and effective; however, the latter is more common in the UK except when sterilization is performed immediately postpartum when the uterus is large, the fallopian tubes are enlarged, the pelvis very vascular and the risks of laparoscopy increased. Laparoscopic sterilization accounts for almost 10% of the gynaecological workload in Scotland.

A variety of techniques exist for occluding the tube and are shown in Table 31.5. The commonest method of tubal occlusion during laparotomy and mini-laparotomy is the Pomeroy technique where a loop of tube is ligated and excised.

**Table 31.5** Female sterilization — methods of tubal occlusion

| | |
|---|---|
| Ligation | Absorbable or non-absorbable sutures<br>The ends left free or buried in the broad ligament or uterine cornu |
| Electrocautery | One or more areas cauterized<br>Bipolar diathermy allows only the tissue held between the jaws of the forceps to be cauterized; the temperature of the tube may reach 400 °C and if it touches adjacent structures can cause local burns<br>Cautery close to the cornua may increase the risk of ectopic pregnancy |
| Falope ring | A ring of silicone rubber is placed over a loop of tube with a specially designed applicator<br>Destroys 2–3 cm of tube |
| Clips | A variety of clips are available; the Hulka–Clemens clip (stainless steel and a polycarbonate) and the smaller Filshie clip (titanium lined with silicone rubber) are the most commonly used<br>Much smaller length of tube destroyed |
| Laser | Carbon dioxide laser divides tube very cleanly but may allow a high incidence of recanalization<br>The Nd-YAG laser is extremely expensive |

Nd–YAG, neodymium–yttrium, aluminium, garnet.

### *Efficacy*

Failures and complications of sterilization are a common cause of litigation among gynaecologists. A prospective study of 10 000 women in the USA (Peterson *et al.* 1996) compared the cumulative pregnancy rate 10 years after sterilization with a variety of different methods. Sterilization using unipolar diathermy and postpartum partial salpingectomy had the lowest failure rates while clips were associated with the highest. The overall pregnancy rate after 10 years was 18.5 per 1000 procedures. In this survey 33% of the pregnancies which occurred (excluding luteal phase pregnancies) were ectopic and the failure rate was higher among women sterilized before the age of 28 years. When conception occurs following diathermy up to 50% may be ectopic compared with only 5% following occlusion with clips or rings; moreover tubal diathermy has the potential for serious complications if adjoining structures (most commonly bowel) are burnt. Rings are associated with a higher risk of haemorrhage from or avulsion of the tube and because of ischaemia of the loop caught in the ring cause much more postoperative pain. Clips destroy less length of tube than rings but the higher failure rate in the USA study may reflect the fact that clip placement is technically more difficult than the application of rings or diathermy. Filshie clips are easier to apply than the Hulka-Clemens variety and allow occlusion of thicker tubes.

A number of chemical agents have been tested for their ability to occlude the fallopian tube when instilled into the tube either directly or transcervically via the uterus. A 252 mg quinacrine pellet is inserted into the uterine cavity through a modified IUD inserter passed through the cervix. Two insertions, 1 month apart, are made during the follicular phase of the cycle. Inflammation and fibrosis causes occlusion of the intramural segment of the tube and a failure rate of 2.6% after 1 year of follow-up is reported. The method is cheap and can easily be performed by non-medical personnel. However, the safety of quinacrine sterilization has not yet been determined and morbidity appears to be higher than with surgical procedures. Although widely used in some parts of Asia, the technique has not been approved in any developed country.

*The timing of female sterilization*

It is seldom possible to arrange sterilization for a particular time of the cycle and women should continue using their current method of contraception until surgery. It is not necessary to stop the combined pill before sterilization as the risk of thromboembolic complications is negligible. If an IUD is *in situ* it should be removed at the time of sterilization, unless the operation is being done at mid-cycle and intercourse has taken place within the previous few days in which case it can be removed after the next menstrual period. The date of the last menstrual period should be checked preoperatively. If there is any concern about pregnancy, a test should be performed. A routine pregnancy test on the day of sterilization significantly reduces the rate of undetected luteal phase pregnancies. Curettage at the time of sterilization is not usually performed, and if it is intended as a means to terminate a luteal phase pregnancy, it might be illegal unless the terms of the Abortion Act are being met. It may also be ineffective since the blastocyst may be missed.

*Immediate complications*

1 The mortality from laparoscopic sterilization is less than 8 per 100 000 operations. The commonest cause of death is anaesthesia.
2 Vascular damage or damage to bowel or other internal organs may occur during the procedure and is usually recognized at the time of operation.
3 Gas embolism.
4 Thromboembolic disease is rare, but more likely immediately postpartum.
5 Wound infection.

It has been suggested that the operative complication rate is higher when sterilization is done at the same time as theraputic abortion; however, the rate is less than that of the two separate procedures added together. There is, however, a two- to fourfold increase in the failure rate.

*Long-term complications*

1 Menstrual disorders — a number of studies have demonstrated an increased incidence of gynaecological consultation and of hysterectomy following sterilization despite no demonstrable change in menstrual blood loss. Changes in menstrual bleeding patterns are inevitable with advancing age and after stopping the combined pill and women who have been sterilized may be more likely to seek or accept hysterectomy as they are no longer capable of child-bearing.
2 Abdominal pain and dyspareunia may occur after sterilization and are said to be more common after cautery. Repeat laparoscopy usually fails to demonstrate any pathology and the symptoms may sometimes be a manifestation of regret.
3 Psychological and psychosexual problems are rare and when they do arise tend to do so in those who have had problems before sterilization. Many studies report a better mental state after sterilization.
4 Bowel obstruction from adhesions is a very rare complication.

VASECTOMY

Division or occlusion of the vas deferens prevents the passage of sperm. The vas can be ligated or occluded with clips or by diathermy. Percutaneous injection of sclerosing agents or occlusive substances such as silicone are used in China. It has been claimed that the silicone plug can be removed and the vasectomy successfully reversed. No one method seems to be more effective than any other but the non-scalpel vasectomy (NSV) which obviates the need for a skin incision is associated with a reduced incidence of haemorrhage and infection.

The success of the procedure is verified by the absence of sperm from two consecutive samples of ejaculate collected at least 4 weeks apart. The time taken for azoospermia to develop depends on the frequency of intercourse; it is estimated that some 20 ejaculations are required and seminal fluid should be examined at 12 and 16 weeks postvasectomy. Contraception must be continued until confirmation of two negative results has been achieved.

*Immediate complications*

1 Scrotal bruising occurs in almost everyone, haematoma (1–2%) and wound infection (up to 5%) are common minor complications.
2 Up to 2% of men fail to achieve azoospermia, in which case the vasectomy needs to be repeated.
3 Even despite two negative seminal fluid samples, failure occurs in 1 in 1000 men up to 10 years after operation.

*Late complications*

1 The development of antisperm antibodies (thought to be in response to leakage of sperm) occurs in most men and appears to be harmless unless restoration of fertility is desired.
2 Small inflammatory granulomas can form at the cut ends of the vas — presumably also in response to leaked sperm. Sperm granulomas may be painful and persistent but can be effectively excised.
3 Concerns have previously been raised linking vasectomy with an increased risk of atherosclerosis, testicular

Table 31.6 Points to cover when counselling for sterilization

| |
|---|
| The reason for the request — some women seek sterilization as a cure for menstrual dysfunction, sexual problems or abdominal pain |
| Family size and the possibility of wanting more children |
| Previous and current contraception and any problems experienced. Some women request sterilization because they are unable to find any other acceptable method of contraception; this is not a good reason for sterilization |
| The stability of the marriage and the possibility of its breakdown |
| The quality of the couple's sex life |
| The procedure |
| The failure rate |
| The risks and side-effects |
| Which partner should be sterilized |
| Reversibility |
| The practical arrangements, e.g. continued use of interim contraception |

cancer and other, mainly autoimmune, diseases. Several large studies have failed to substantiate these concerns (see Glasier 1995 for review). However, an increased risk of prostate cancer has also been suggested. Only epidemiological evidence is available and there seems to be no biological plausibility for such a link. Nevertheless, further research is required.

*Counselling for sterilization*

Most couples seeking sterilization have been thinking about the operation for some considerable time. The initial consultation should cover a number of points (Table 31.6).

*Reversal of sterilization*

Whilst as many as 10% of couples may regret being sterilized, only 1% request reversal. Couples sterilized at a young age, immediately postpartum or after theraputic abortion are more likely to experience regret. A change of partner is the commonest reason for requesting reversal. More than 1 in 3 marriages end in divorce in the UK and many couples now do not bother to get married. The stability of the couple's relationship should be explored during counselling.

Reversal of female sterilization involves laparotomy, may fail (microsurgical techniques are associated with around 70% success) and carries a significant risk of ectopic pregnancy (up to 5%). Ovulation should be confirmed and a normal semen analysis obtained before reversal is undertaken. Reversal of vasectomy is technically feasible in many cases with patency rates of almost 90% being reported in some series. Pregnancy rates are much less (up to 60%) perhaps as a result of the presence of antisperm antibodies.

## Barrier methods

Barrier methods work by preventing the passage of sperm into the female genital tract.

### MALE AND FEMALE CONDOMS

The male condom remains one of the most popular methods of contraception. It is cheap, widely available over the counter and with the exception of the occasional allergic reaction is free from side-effects. Most condoms are made of latex, the newly available plastic condom Avanti is said to be less allergic and to confer better sensation. It is more robust to storage in extreme temperature but is very much more expensive. Use of the condom has increased significantly during the last decade as a result of concern over the spread of human immunodeficiency virus.

In addition to protection against sexually transmitted diseases, use of the condom — and diaphragm — is associated with a significant reduction in cervical disease including cancer.

Most condoms are lubricated with spermicide. Spermicides are agents which are capable of destroying sperm usually incorporated into an inert base which itself may impair sperm mobility. The commonest is nonoxynol-9, a non-ionic surfactant which alters sperm surface membrane permeability causing osmotic changes and death.

Spermicides are also available as creams, jellies, foaming tablets, pessaries and aerosols (which are very expensive). Used alone spermicides have a high failure rate (see Table 31.1) but may be useful for women in the perimenopause who have intercourse infrequently and who are at a very low risk of pregnancy.

Laboratory tests indicate that nonoxynol-9 inactivates many sexually transmissible pathogens including *Chlamydia*, *Neisseria gonorrhoeae* and HIV. *In vivo*, however, when used in high doses (as by sex workers) nonoxynol-9 may in fact facilitate the transmission of HIV.

The female condom is a polyurethane sheath, the open end of which is attached to a flexible polyurethane ring. A removable ring inside the condom acts as an introducer and helps keep the device inside the vagina. It is available in one size with a non-spermicidal lubricant. It is designed for single use and is expensive. Failure rate are similar to those of the male condom (see Table 31.2). Its primary aim is to prevent sexually transmitted diseases, but the female condom has not become popular.

#### DIAPHRAGM AND CERVICAL CAP

The diaphragm (and cap) are less popular than male condoms. They must be fitted by a doctor or nurse and do not confer the same degree of protection from HIV. Selecting the correct size of diaphragm is similar to selecting the right size of vaginal ring for the management of vaginal prolapse. On vaginal examination with the middle finger in the posterior fornix the point at which the symphysis pubis abuts the ulnar border of the index finger is noted. The distance between that point and the tip of the middle finger is a guide to the appropriate size.

### Natural family planning

Few couples in the UK use so-called natural methods of family planning (NFP) although in some parts of the world these methods are common. All involve the avoidance of intercourse during the fertile period of the cycle (periodic abstinence). Methods differ in the way in which they recognize the fertile period. The simplest is the calendar or rhythm method in which the woman calculates the fertile period according to the length of her normal menstrual cycle. The first day of the fertile period is calculated as being the length of the woman's shortest cycle minus 20 days, and the last day of the fertile period is the longest cycle minus 11 days. If therefore cycle length varies from 25 to 31 days the potential fertile period and days when intercourse should be avoided are days 5–20.

Other approaches use symptoms which reflect fluctuating concentrations of circulating oestrogen and progesterone. The mucus or Billings method relies on identifying changes in the quantity and quality of cervical and vaginal mucus. As circulating oestrogens increase with follicle growth, the mucus becomes clear and stretchy allowing the passage of sperm. With ovulation, and in the presence of progesterone, mucus becomes opaque, sticky and much less stretchy or disappears altogether. Intercourse must stop when fertile-type mucus is identified and can start again when infertile type mucus is recognized. Progesterone secretion is also associated with a rise in basal body temperature (BBT) of about 0.5 °C. The BBT method is thus able to identify the end of the fertile period. Other signs/symptoms such as ovulation pain, position of cervix and degree of dilatation of the cervical os can be used additionally to help define the fertile period.

A hand-held monitor with disposable urine dip sticks is available in the UK to facilitate accurate detection of the fertile phase of the cycle. Persona measures urinary concentrations of oestrone-3-glucuronide and LH and the ratio between the two hormones is used to define the start and the end of the fertile phase. A red light is displayed on days when intercourse should be avoided. Failure rates are said to be around 6%. The devise is expensive and not available on the NHS.

Whatever method is used many couples find it difficult always to abstain from intercourse during the fertile period. Failure rates are high (see Table 31.1) and most of the failures are due to conscious rule breaking. Perfect use of the mucus method is associated with a failure rate of only 3.4%. In a multicentre study of the mucus method, couples who had completed their families had lower failure rates than couples who were using NFP as a method of birth spacing.

There is no evidence that pregnancies occurring among NFP users which are conceived with ageing gametes (i.e. towards the end of the fertile period) are associated with a higher risk of congenital malformations.

#### LACTATIONAL AMENORRHOEA METHOD

During the 1980s there was an increased interest in the contraceptive effects of breast-feeding. Breast-feeding delays the resumption of fertility after childbirth and the length of the delay is related to the frequency and duration of breast-feeding episodes and the timing of the introduction of food other than breast milk. In countries where prolonged breast-feeding occurs, ovulation and therefore the risk of pregnancy may be postponed for more than a year. In 1988 at a consensus conference held in Bellagio, Italy, scientists pooled clinical and endocrine data obtained from 13 prospective studies undertaken in both developed and developing countries. They agreed that a woman who is fully or nearly fully breast-feeding and who remains amenorrhoeic has less than a 2% chance of pregnancy during the first 6 months after childbirth. The Bellagio guidelines were subsequently formalized into a method of family planning known as the lactational amenorrhoea method (LAM). LAM is actually an algorithm (Fig. 31.2) which enables a woman to determine whether or not her pattern of infant feeding combined with her pattern of menstruation, confers effective contraception.

Since 1988 two studies have tested LAM prospectively and demonstrated failure rates of 0.5–0.6%. In developed countries where average durations of breast-feeding are short and where few women practice full or nearly full breast-feeding beyond 4 months postpartum, LAM is unlikely to be a practical method of contraception. In developing countries, however, where women breast-feed for much longer, and where modern methods of contraception may be expensive and difficult to obtain, the potential for LAM is much greater.

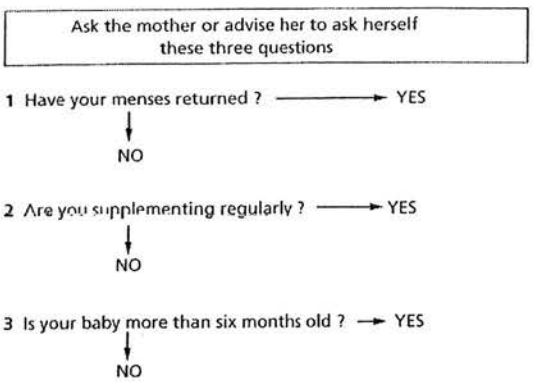


**Fig. 31.2** The algorithm for the use of the lactational amenorrhoea method (LAM).

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## REVIEW ARTICLE

**DRUG THERAPY**

ALASTAIR J.J. WOOD, M.D., *Editor*

# HORMONAL CONTRACEPTION

DAVID T. BAIRD AND ANNA F. GLASIER

THE discovery that progesterone blocked ovulation and the development of the combined oral contraceptive pill in the 1950s were landmarks in the control of human fertility.[1,2] By providing women with a reliable method of regulating their fertility, the combined oral contraceptive has played an essential part in allowing them to participate fully in society. In spite of initial alarm that it would lead to sexual promiscuity and moral degeneration, the use of hormonal steroids rapidly became widespread and is the most popular method of contraception in most Western countries.[3]

## METHODS OF HORMONAL CONTRACEPTION

Hormonal contraceptive steroids are available mainly as oral preparations, although preparations for subcutaneous implantation and vaginal insertion have also been developed[4] (Table 1). Combined oral contraceptives are a mixture of a synthetic estrogen (e.g., ethinyl estradiol) and one of several C-19 steroids with progestational activity (e.g., norethindrone). Most of the oral contraceptives contain a fixed dose of estrogen and progestogen and are taken daily for 21 days, followed by 7 days without treatment. They are highly effective, with pregnancies occurring at rates of only 0.1 to 1.0 per 100 woman-years of use. They inhibit ovulation and induce changes in cervical mucus and the endometrium that make sperm transport and implantation of the embryo, respectively, unlikely. Triphasic preparations, which contain both estrogen and progestogen, but in varying proportions, were introduced to reduce the total monthly dose of progestogen and mimic more closely the hormonal changes of the menstrual cycle. The dose of estrogen had to be increased, however, to inhibit ovulation reliably. These preparations offer little if any advantage over the monophasic pills.

Administering a small dose of progestogen (norethindrone or levonorgestrel) every day provides an estrogen-free method of contraception. Ovulation is inhibited in only about half the women who take an oral progestogen; the principal mode of action is their ability to make cervical mucus hostile to the transport of sperm. Contraceptives containing only progestogen are less effective than combined oral contraceptives (about 3.0 pregnancies per 100 woman-years), and their use is often restricted to women whose fertility is already reduced, such as older or lactating women and women in whom a combination oral contraceptive is contraindicated. Progestogens given intramuscularly inhibit ovulation more often than those given orally, but progestogens cause menstrual disturbances as often as oral preparations (see below).

Although the efficacy of hormonal contraception was rapidly established, it took longer to determine its safety and acceptability. In an attempt to reduce side effects, the doses of estrogen have been reduced by 80 percent or more, and new progestogens and different routes of administration have been explored. Although contraceptives given to large numbers of healthy women must be as safe as possible, any potential risk has to be weighed against the hazards associated with pregnancy resulting from unprotected intercourse or the use of a less effective method.[5] In this review we shall discuss the risks and benefits of hormonal contraception. In addition, we shall highlight the most recent developments, including alternative methods of delivery and the use of nonsteroidal compounds.

## DEVELOPMENTS IN COMBINED ORAL CONTRACEPTION

Since the mid-1960s, ethinyl estradiol has been the estrogen in almost all combined oral contraceptives, but the amount has progressively decreased; most preparations now contain 35 μg or less.[5] In contrast, in response to the desire to minimize the associated androgenic side effects, the type of synthetic progestogen has been changed. The newest, so-called third-generation, progestogens (desogestrel, gestodene, and norgestimate) are extremely potent in their ability to inhibit ovulation and transform estrogen-primed endometrium into secretory endometrium.[6] They are weak antiestrogens, have less androgenic activity than their predecessors,[7] and are associated with fewer changes in lipoprotein metabolism and perhaps carbohydrate metabolism.[8]

## RISKS OF COMBINED ORAL CONTRACEPTIVE AGENTS

A 1969 editorial in the *Lancet* concluded that the wisdom of administering oral contraceptives to healthy women for many years should be seriously questioned.[9] Twenty-four years later it is clear that combined oral contraceptive agents are an extremely

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Table 1. Hormonal Contraceptive Agents.

| TYPE | AGENT AND DOSE | MODE OF ADMINISTRATION |
|---|---|---|
| Combined oral agent | Ethinyl estradiol (30 μg)<br>Desogestrel (150 μg) | Daily oral administration for 21 days, with 7-day hiatus |
| Oral progestogen only | Norethindrone (350 μg) | Daily oral administration |
| Injectable depot progestogen | Medroxyprogesterone acetate (150 mg) | Intramuscular injection every 12 wk |
| Combined-agent vaginal ring | Ethinyl estradiol (15 μg/day)<br>Desogestrel (150 μg/day) | Vaginal insertion for 21 days, with 7-day hiatus |
| Progestogen-only vaginal ring | Levonorgestrel (20 μg/day) | Vaginal insertion |

effective and safe method of contraception, but despite extensive research the long-term risks are not entirely clear.

### Endometrial and Ovarian Cancer

Combined oral contraceptives have a protective effect against both cancer of the ovary and cancer of the endometrium. In a study of women who took oral contraceptives containing high doses of estrogen and progestogen for 2 years, the relative risk of endometrial cancer was reduced to 0.4 and the protective effect lasted for at least 15 years.[10] Whether preparations containing lower amounts of estrogen and progestogen would provide equivalent protection is less clear, but if the mechanism of action involves the maintenance of regular withdrawal bleeding it is unlikely that the lower doses would be any less effective. If lower doses enable women to continue to use one of these agents well beyond the age of 35 years, the risk of endometrial cancer may be further reduced.

In studies of ovarian cancer and the use of oral contraceptives, there was a dose-dependent decrease in the relative risk to 0.2 after 10 years of use (as compared with the risk in women who had never used oral contraceptives).[11] The effect was still apparent 15 years after discontinuation of the agent. The mechanism of protection against ovarian cancer is unclear.

### Liver Cancer

There is a relatively close correlation between infection with hepatitis B virus and cancer of the liver in areas of the world where this infection is common.[12] In these areas the short-term use of combined oral contraceptives is not associated with an increased risk of liver cancer, but there are few data on long-term use. In contrast, in areas where cancer of the liver is uncommon, an association has been established; whereas the relative risk was 1.0 for women who had ever used an oral contraceptive, it was 4.4 for those who had used one for eight years.[12]

### Cancer of the Cervix

The relation between the use of oral contraceptives and cancer of the cervix is not clear. Use is associated with endocervical hyperplasia, which is probably caused by the progestogen component and is dependent on the dose and duration of use.[13] Some reports have suggested a relation between oral contraceptives and cervical adenocarcinoma in young women, but the cancer is uncommon. There is a small increase in the risk of squamous carcinoma of the cervix (relative risk, 1.3 to 1.8) in women who have taken an oral contraceptive for more than five years.[14] However, both types of cervical cancer are highly correlated with sexual activity. After differences in sexual activity and the use of barrier methods of contraception (which have a protective effect) have been accounted for, there appears to be no increase in the risk of cervical cancer among women who take a combined oral contraceptive.

### Breast Cancer

The case for a relation between oral contraceptives and breast cancer is more difficult to dismiss. Estrogen stimulates the growth of breast tissue, and long-term estrogen administration may reasonably be expected to be associated with an increased risk of breast cancer, as has been reported in postmenopausal women.[15] A recent meta-analysis of 16 case–control studies concluded that there was a 1.3-to-1.8-fold increase in the risk of breast cancer among women taking estrogen for more than 10 years.[16] Despite numerous studies, the question of an association between combined oral contraceptives and breast cancer remains unresolved. Four large prospective studies, two from the United Kingdom and two from the United States, and a large case–control study by the Cancer and Steroid Hormone Study Group in the United States have had the most influence on our thinking about this subject.[17-21] In these studies and a meta-analysis of these and all other studies in the English and French literature since 1975,[22] there was no increase in the risk of breast cancer in women who had ever taken an oral contraceptive. The same was true in the studies reported after 1980, which were performed among women taking the oral contraceptive preparations now in use. A World Health Organization scientific group recently concurred with this conclusion and recommended no change in family-planning policies regarding the use of oral contraceptives.[12] Moreover, there has been no increase in the incidence of breast cancer attributable to the use of combined oral contraceptives in the United Kingdom, according to data from various national cancer registries.[23]

The same meta-analysis, however, confirmed the conclusions of the U.K. National Case–Control Study Group that the risk of breast cancer before the age of 46 years is increased by 46 percent among women who have taken a combined oral contraceptive for at least 10 years.[18,22] The most relevant period of exposure may be between menarche and the first full-term pregnancy. In the United Kingdom the cumulative incidence of breast cancer is 1 in 500 by the age of 36 years. The increase in risk calculated by the U.K.

National Case–Control Study Group should therefore be discernible from cancer-registry data, but it is not.[23] Furthermore, there is no relation between dose or duration of use and the risk of cancer.

#### Cardiovascular Disease and Lipid Metabolism

Large cohort studies in the United Kingdom have examined the relation between cardiovascular disease and the use of combined oral contraceptives.[24,25] In 1977 the Oxford Family Planning Association Contraceptive Study demonstrated a 4.7-fold increase in the risk of death from cardiovascular disease among women using oral contraceptives containing 50 μg of estrogen.[24] It is clear that a reduction in the dose of estrogen is associated with a reduction in this risk. In the more recent prospective Nurses' Health Study the relative risk of cardiovascular disease among women who had ever used an oral contraceptive was 0.8.[26] The risk of cardiovascular disease associated with the use of combined oral contraceptives is often attributed to changes in serum concentrations of lipoproteins, and there have been more than 100 published reports on the effect of combined oral contraceptives on serum lipoprotein concentrations. In a recent review of six formulations, Fotherby[27] concluded that they did not change total serum cholesterol concentrations but did increase triglyceride concentrations, and those containing some of the newer progestogens also increased serum levels of high-density lipoprotein cholesterol.

There is no evidence that formulations containing low doses of estrogen are associated with an increased risk of cardiovascular disease. The issue of changes in lipid metabolism associated with the use of oral contraceptives is complex, and the association between the changes in serum lipoprotein levels and cardiovascular disease is indirect. Each of the three major lipoprotein classes contains a number of discrete subfractions with different biologic characteristics,[28] and much of the evidence of a link between cardiovascular disease and serum lipoproteins comes from studies among men rather than young women. Estrogen may actually protect against cardiovascular disease by a direct action on arterial walls that protects them against atheromatous injury. The reversal of the beneficial effects of estrogen on lipoprotein metabolism produced by the addition of a progestogen may therefore be irrelevant. Moreover, the risk of cardiovascular disease in premenopausal women probably results not from premature atherogenesis but from thrombogenesis, the risk of which is related to many variables. These variables include not only serum lipoprotein concentrations but also changes in procoagulants and platelet aggregation.[29] Combined oral contraceptives increase the production of factor X, factor II, and plasminogen; decrease the production of antithrombin; and increase platelet aggregation by reducing the production of prostacyclin.[30] These changes are probably important only in women who smoke, since smoking also increases the risk of thrombogenesis.

We conclude that combined oral contraception is safe in women who do not have preexisting disease of the circulatory system. It is almost certainly preferable that they not smoke. In the absence of other risk factors, however, the combination of smoking and use of an oral contraceptive is probably safe.

#### Glucose Tolerance

In contrast to estrogens, progestogens impair glucose tolerance, the degree of impairment depending on both the type and the dose.[31] The impairment is most marked with nandrolone derivatives and least with medroxyprogesterone acetate.[32] The third-generation progestogens have little if any effect on carbohydrate metabolism. Moreover, most women whose glucose metabolism becomes abnormal after they begin taking a combined oral contraceptive have normal glucose tolerance after six months of use. These agents may increase insulin requirements in women with diabetes mellitus, however. The need to increase the dose of insulin may be a small price to pay for reliable contraception in women in whom pregnancy may be contraindicated.

#### Hypertension

Combined oral contraceptives cause hypertension in about 4 to 5 percent of normotensive women and increase blood pressure in about 9 to 16 percent of women with preexisting hypertension.[33] The effect is probably due to both hormones, and the risk is related to race, family history, obesity, diet, smoking, and the duration of the use of the oral contraceptive agent. Some of the third-generation progestogens may have an antimineralocorticoid effect and thus be associated with a reduced risk of hypertension.[6] Monitoring blood pressure during the first three months of use allows one to identify affected women. The effect is almost always reversible.

### Contraception with Progestogen Only

Contraception with progestogen alone is the only hormonal alternative to the use of a combined oral contraceptive. It would be expected to have fewer systemic side effects, but it is associated with a high incidence of disturbances in menstruation, particularly irregular bleeding.[34-36] There are no data on the long-term risks of contraception with progestogen alone. Only 8 percent of the women in the United Kingdom who use contraception, and even fewer in the United States, take an oral progestogen-only contraceptive.[3,37] Most are older women or women in whom estrogen is contraindicated.[38] The use of progestogen-only contraception by older women is likely to decrease as the dose of estrogen in combined oral contraceptives is reduced and as the recommendation that combined oral contraceptive agents are safe for nonsmoking women over the age of 35 years becomes widely accepted.[39] Progestogen-only contraception is widely used by breast-feeding women in the United King-

dom, since progestogen — unlike estrogen — does not affect lactation.[40] In the United States and Australia, lactation is still considered a contraindication to contraception with progestogen only.

Progestogens have no effect on blood clotting or platelet aggregation and are the contraceptive of choice for women with hypertension.[41] The older progestogens impair glucose tolerance slightly but not enough to increase insulin requirements in women with diabetes.[32]

An injectable progestogen-only agent, depot medroxyprogesterone acetate, has been available in the United Kingdom and was recently licensed in the United States (Table 1). It offers an extremely effective and safe method of contraception.[42] In a large World Health Organization case–control study involving 869 women with breast cancer and 11,870 controls, the relative risk of breast cancer among women who had ever used depot medroxyprogesterone was 1.2 (95 percent confidence interval, 1.0 to 1.5).[43,44] The results of a small study from New Zealand reporting a significant loss of bone mineral density in long-term users were confounded by the effects of smoking.[45]

### New Delivery Systems

Steroidal contraceptives are highly effective, relatively safe, and easy to use. Prospects for the development of new nonsteroidal methods seem limited. Recent research has concentrated on the development of new systems for delivering steroidal contraceptive agents. Nonoral routes offer the advantage of avoiding the first pass through the liver, thereby allowing lower doses of hormone and reducing metabolic side effects, and they produce constant serum hormone concentrations and simplify compliance.[46] A subcutaneous implant of levonorgestrel (Norplant) was approved for use in the United States in 1990 and will probably be approved in the United Kingdom this year. The implant, designed to be replaced after five years, consists of six nonbiodegradable silicone-rubber capsules containing a total of 36 mg of levonorgestrel[47] that release an average of 30 μg per day. The rates of failure rise from 0.04 percent in the first year to 1.1 percent in the fifth year, and they are higher in obese women.[48] This preparation, like all progestogen-only agents, is associated with a relatively high incidence of menstrual irregularities, and after three years 50 percent of women have discontinued the method, which requires surgical removal of the implant.

The progestogen-only vaginal ring releases 20 μg of levonorgestrel per day and is designed to last for three months. Its use is associated with failure rates similar to those of oral progestogen-only agents.[49] Up to 17 percent of women discontinue use because of menstrual irregularities. Much better cycle control is achieved with the combined-agent vaginal ring, which releases 15 μg of ethinyl estradiol and 120 μg of desogestrel per day and is worn for 21 days and removed for 7 days.[50] Failure rates are similar to those of combined oral contraceptives. Many women find the combined-agent vaginal ring an acceptable method. The long-term effect of relatively high doses of gonadal steroids in close proximity to the vagina and cervix is not known.

### Postcoital Contraception

The concept of a method of contraception that could be used after intercourse is not new and has many attractions.[51] High-dose estrogen alone (e.g., 25 mg of diethylstilbestrol per day for five days) or combined with a progestogen (100 μg of ethinyl estradiol plus 1 mg of levonorgestrel twice a day at 12-hour intervals) has been successful in reducing the risk of pregnancy after unprotected intercourse. The efficacy of these methods is hard to judge, but postcoital contraception probably reduces the risk of pregnancy by 90 to 95 percent.[52] There are no serious side effects, but the relatively high incidence of vomiting and disturbed menstrual cycles and the fact that the medication must be taken within 72 hours after intercourse have limited the widespread use of these regimens. A single 600-mg dose of mifepristone (RU 486) appears to be highly effective as a postcoital contraceptive.[53] Even if further studies confirm its efficacy, however, there remains the problem of how to make it widely available while at the same time preventing its unauthorized use as an abortifacient.

### Hormone-Impregnated Intrauterine Devices

Hormone-releasing intrauterine devices have attracted interest for more than a decade. Initial problems with an increased risk of ectopic pregnancy appear to have been overcome by increasing the dose of synthetic progestogen.[54] A levonorgestrel-impregnated intrauterine device that releases 20 μg of levonorgestrel per day has been developed in Scandinavia.[55] The hormone is placed in a Silastic capsule on a standard polyethylene frame. The cumulative rate of pregnancy after seven years of continuous use was reported to be 1.1 percent. As compared with inert or copper intrauterine devices, the device reduces menstrual blood loss, and many women become amenorrheic after the first few months of use.[56] Amenorrhea is due to endometrial atrophy, and possibly to the destruction of endometrial estrogen receptors. Ovarian function is only infrequently affected, and 75 percent of women continue to ovulate.[57] Thus, amenorrhea is not accompanied by hypoestrogenism. In addition to being a very effective contraceptive that may be attractive to older women with menstrual irregularities, the progestogen-impregnated intrauterine device opens new possibilities for the noninvasive management of menorrhagia regardless of the need for contraception.[58]

### Male Contraception

The development of reliable methods of hormonal contraception has proved much more difficult for men than for women.[59] The regulation of spermatogenesis is poorly understood, and the link between sexual ac-

tivity and hormones is much more direct in men than in women. Any method that compromises the endocrine activity of the testes must also involve testosterone replacement if sexual function is to be maintained. The use of large amounts of testosterone to inhibit the secretion of follicle-stimulating hormone and luteinizing hormone and hence spermatogenesis is not new.[59] As early as 1950 azoospermia was achieved by the daily injection of 25 mg of testosterone proprionate.[60] It is necessary to give testosterone by injection because orally active synthetic androgens such as methyltestosterone may cause liver damage. More recently, there has been widespread publicity concerning the use of testosterone enanthate given weekly in a dose of 200 mg intramuscularly.[61] Complete azoospermia occurred in only 157 of 271 men, and it was more likely in Asian men than white men. The combination of a potent antagonist of gonadotropin-releasing hormone and testosterone causes azoospermia more often,[62] but the need for daily injections of antagonist makes this regimen impractical. Moreover, potential changes in clotting factors, enlargement of the prostate, and changes in serum lipoproteins raise concern about the long-term risks of such a treatment.[63] The prospects for a male contraceptive seem as distant as ever.

## New Developments

The most promising development in the field of hormonal contraception has been the use of hormone agonists and antagonists.[64] Agonists of gonadotropin-releasing hormone bind to gonadotropin-releasing hormone receptors on the anterior pituitary and, after initially stimulating the secretion of follicle-stimulating hormone and luteinizing hormone, produce a hypogonadotropic state by down-regulation of the receptors. Ovulation is inhibited during chronic intranasal administration of the gonadotropin-releasing hormone agonist buserelin.[65] This agent could prove particularly useful as a contraceptive during breast-feeding, since minimal quantities pass into the milk.[66] If ovarian activity is completely suppressed, however, the deleterious effects of a prolonged hypoestrogenic state on bone and the cardiovascular system would probably necessitate some form of replacement therapy. On the other hand, incomplete suppression with residual ovarian activity might lead to an increased risk of endometrial hyperplasia and cancer due to the effects of unopposed estrogen.

Antagonists of progesterone offer considerable potential for the regulation of fertility.[67] Progesterone is essential for a range of reproductive functions, including the establishment and maintenance of pregnancy. Antagonists of progesterone, such as mifepristone, block the action of progesterone on the endometrium and hence produce an environment hostile to pregnancy. Mifepristone in combination with a prostaglandin is a highly effective and safe method for the termination of early pregnancy.[68] The political controversy surrounding this agent has overshadowed its potential use as a contraceptive. When given in the early luteal phase of the cycle it prevents the development of a secretory endometrium, and preliminary trials indicate that it may be effective when given at that time as a once-a-month contraceptive.[69,70]

The ability of mifepristone to block ovulation when given in the follicular phase of the cycle[71] and to prevent the development of a secretory endometrium in the luteal phase probably explains its efficacy as a postcoital agent.[52] Continuous administration in daily doses as low as 1 mg inhibits ovulation, suggesting that it may be a useful alternative to contraception with progestogen alone.[72,73]

## Conclusions

The current methods of hormonal contraception have been in clinical use for more than 30 years and have proved to be highly reliable and acceptable to many millions of women. Overall, the health benefits of these methods far outweigh their side effects and risks. Of the many difficulties involved in the development of new methods of contraception, a major hurdle is the insistence by some regulatory authorities that there be absolute proof of long-term safety. This ideal goal is virtually impossible to achieve; it requires, as Sir Alan Parkes put it, that "no woman should be kept on the Pill for 20 years until, in fact, a sufficient number of women have been kept on the Pill for 20 years."[74] In 1993 the evidence suggests that after risk factors (e.g., smoking, hypertension, and obesity) have been identified, combined oral contraceptives are safe for most women for most of their reproductive lives. The incidence of cancer of the ovary, uterus, cervix, and breast is related to the pattern of ovarian and sexual activity throughout reproductive life, not to the use of contraceptives.[75] It has been proposed that by manipulating the hormonal environment with gonadotropin-releasing hormone agonists and estrogen-replacement therapy, it may be possible to provide contraception while at the same time reducing the risk of cancer of the reproductive system and death from cardiovascular disease.[76] Although the practical problems associated with developing such radical approaches are considerable, the principal constraints on the application of novel methods of hormonal contraception are not likely to be medical or scientific. As Fathalla states, "For research to have an impact on reproductive health, it must be backed up by political commitment and by the provision of adequate resources for health services."[77]

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# Oxford Textbook of Endocrinology and Diabetes

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* = Key reviews.

## 8.1.2 Hormonal contraception

*Anna Glasier*

Hormonal contraception can conveniently be divided into methods which contain both oestrogen and progestogen and methods which contain only progestogen.

### Combined oestrogen–progestogen contraception

Combined hormonal contraception is available as an oral preparation (the combined oral contraceptive pill, COC), an injectable preparation, transdermal patch and contraceptive vaginal ring. The patch is presently still under development but is likely to become available in 2002. Combined injectables are licensed for use in a number of countries, mainly in South America, but are not marketed in the UK.

### Combined oral contraception

Introduced in the early 1960s, the COC has been used by hundreds of millions of women worldwide. In the United Kingdom around 35 per cent of women using a method of contraception take an oral contraceptive pill.

### Available preparations

The combined pill contains oestrogen – almost always ethinyl oestradiol, although there is still one brand available in the UK which contains mestranol – and a progestogen. The dose of oestrogen varies from 50 to 20 μg. Most women now use the so-called 'low dose pill' containing 30–35 μg which are considered to be safer since the cardiovascular risks of the pill are mainly due to oestrogen and, for some conditions, are dose-dependent. However the lower the dose of oestrogen, the higher the chance of poor cycle control, breakthrough bleeding and pregnancy if compliance is poor.

Progestogens are synthetic compounds which bind to the progesterone receptor and behave like the natural hormone. The progestogens used in currently available pills fall broadly into three groups: first generation progestins such as norethindrone, second generation norgestrel derivatives such as levonorgestrel (LNG) and the third generation series including gestodene, desogestrel and norgestimate. Different progestogens have different potencies and equivalent contraceptive effectiveness is achieved at different doses. Third generation progestogens are less androgenic than their predecessors.

Most COC brands are taken for 21 days followed by a seven-day break (the pill free interval or PFI) during which time withdrawal bleeding usually occurs.

Combined pills are available in monophasic preparations in which every pill in the packet contains the same dose of steroids, biphasic and triphasic preparations where the dose of both oestrogen and progestogen changes once or twice during the 21 days. Phasic pills were introduced in order to reduce the total dose of progestogen and in the belief that a regimen which mimicked the normal cycle would produce better cycle control and fewer side effects. There is no evidence for better cycle control and some women find phasic preparations confusing, particularly if they want to run a number of packets of pills together, for example, to postpone menstruation. Every day (ED) preparations are widely used in the USA and Australia where, rather than seven days without pills, women take an inactive tablet. In some countries the inactive tablet contains iron. It is thought that ED pills improve compliance since it is easier to remember to take a pill every day rather than for 21 out of 28 days.

### Mechanism of action

The combined pill acts mainly by inhibiting ovulation. Oestrogen inhibits pituitary FSH secretion thereby suppressing folliculogenesis while the progestogen inhibits the development of the luteinizing

hormone surge. In some women the seven-day PFI is long enough to allow follicle growth and 25 per cent of women will have ultrasound evidence of follicles of 10 mm in diameter on the last day of the PFI. If the PFI is prolonged beyond seven days, these follicles will continue to develop and, despite restarting the pill, ovulation may occur. For women who appear to have conceived as a result of a genuine pill failure (rather than as a result of an error in pill taking) and who wish to continue using the pill , the PFI can be shortened to 4 or 5 days to ensure suppression of follicular development. In the USA a pill has recently been marketed containing 20 μg ethinyl oestradiol and 150 μg desogestrel for 21 days followed by 5 days of 10 μg ethinyl oestradiol alone and two days of a placebo tablet. This regimen suppresses follicular development (as measured by ultrasound) more effectively[1] than a regimen with the standard seven day PFI.

In addition to inhibiting ovulation, the COC alters the characteristics of cervical mucus, thereby impairing sperm transport. Ovum transport may be impaired by an effect on tubal motility. The COC also probably alters endometrial factors essential for uterine receptivity, and causes endometrial atrophy, inhibiting implantation.

## Efficacy

Used perfectly, the COC is almost 100 per cent effective (Table 1). The failure rate with perfect use is 0.1 per 100 woman years (HWY). Women who do conceive despite perfect use may metabolize ethinyl oestrogen more rapidly than usual (so called 'fast acetylators') thereby reducing the effective half-life of the pill. In practice, because of errors in pill-taking, the typical failure rate is 0.2–3 per HWY or higher depending on the population studied.

## Advantages of the combined pill

In addition to being a highly effective method of contraception which women find very easy to use, the COC confers a number of health benefits. Menstrual periods tend to be lighter, shorter and more regular during pill use and dysmenorrhoea and pre-menstrual symptoms are less troublesome. The combined pill is often the first choice of treatment for menorrhagia, dysmenorrhoea, pre-menstrual syndrome and anovulatory dysfunctional uterine bleeding. In developing countries where anaemia is common, COC use reduces the incidence of iron deficiency anaemia through decreased menstrual blood loss.

Other benefits include a decreased incidence (during pill use) of benign breast lumps, functional ovarian cysts, endometriosis, possibly pelvic inflammatory disease and certainly acne.

**Table 1** Percentage of women experiencing unplanned pregnancy during the first year of use of hormonal contraception

| Method | Perfect use | Typical use |
|---|---|---|
| Combined pill | 0.1 | 1–3 |
| Progestogen only pill | 0.5 | 2–5 |
| Depo-Provera | <0.1 | |
| Implant | 0.05 | |
| Mirenon | 0.0 | |
| IUG-IUS | 0.1 | |

There is convincing evidence that the COC protects against both ovarian and endometrial cancer.[2] There is a 50 per cent reduction in the risk of epithelial ovarian cancer after five years use of the COC which persists for at least ten years after pill use stops. The mechanism for the protective effect is unclear but may be related to the reduction in the total number of ovulations, and therefore rupture of the ovarian capsule, experienced in a lifetime. In the recent analysis of 25 years of follow-up of 46 000 women who took part in the Royal College of General Practitioners' (RCGP) Oral Contraceptive Study[3] which compared 517 519 years of pill use with 335 998 years of never-use, the relative risk of death from ovarian cancer was reduced to 0.2 (confidence interval 0.2–0.8, $p=0.01$) among women who were using the COC or who had stopped less than ten years ago.

The COC similarly reduces the risk of endometrial cancer, with an effect strongly related to the duration of use. The risk is reduced by 20 per cent after one year and by about 50 per cent after four years. The protective effect seems to be sustained for perhaps as long as 15 years after stopping the pill. In the RCGP study, although the risk of death from endometrial cancer was reduced among current and recent (within ten years) users, the extent of the reduction did not reach statistical significance, probably because the sample size was inadequate and because the average age of the women at the time the data were analysed was 49 years, relatively young to develop endometrial cancer.

## Contraindications

The absolute contraindications to the COC are listed in Box 1.

Relative contraindications include the presence of serious, or multiple, risk factors for arterial disease – hypertension; family history; diabetes mellitus; smoking; increasing age; obesity and migraine. Oestrogen stimulates prolactin production and women with hyperprolactinaemia wishing to avoid pregnancy should be advised to use progestogen-only contraception.

In 1995 the World Health Organisation (WHO) produced an evidence-based document listing all commonly available methods of contraception together with criteria for their use in the presence of certain medical conditions. It was revised in 2000 taking into account new data published since 1995. This second edition of the so called Medical Eligibility Criteria[4] is a useful resource for anyone trying to decide whether a particular method of contraception is appropriate for an individual with a pre-existing medical condition.

## Risks and side effects

The combined pill has an effect on almost every system in the body. Most side effects are minor. Mood change, weight gain, fluid retention, nausea or vomiting, headache, chloasma, loss of libido, mastalgia, breast enlargement and greasy skin are all quite common complaints among pill users. Many improve or disappear within six months of starting the pill but side effects often lead to discontinuation of the method. Since some may be alleviated by a different dose of oestrogen or type of progestogen, it is worth trying another brand if time alone does not solve the problem.

Contraceptive steroids are metabolized by the liver and affect the metabolism of carbohydrates, lipids, plasma proteins, amino acids, vitamins and clotting factors. The COC slightly increases circulating

**Box 1 Absolute contraindications to the combined oral contraceptive pill**

- Ischaemic heart disease including cardiomyopathy
- Most types of valvular heart disease
- Arterial thrombosis
- Venous thrombosis or known predisposition to thrombosis
- Past cerebral haemorrhage and current transient ischaemic attacks
- Vascular malformations of the brain
- Pulmonary hypertension
- Severe hypertension with systolic more than 160 mmHg and/or diastolic more than 100 mmHg
- Hyperlipidaemia
- Focal and crescendo migraine and migraine requiring ergotamine treatment
- Active liver disease, recurrent cholestatic jaundice and Dubin-Johnson or Rotor syndrome
- Liver tumour
- Known gall stones
- Porphyria
- History of serious condition known to be affected by steroids, for example, trophoblastic disease
- Pregnancy
- Undiagnosed genital tract bleeding
- Oestrogen-dependent neoplasms for example, breast cancer

concentrations of triglycerides and low-density lipoproteins (LDL). Combined pills containing levonorgestrel or norethisterone decrease concentrations of high-density lipoproteins (HDL), however HDL is slightly increased among women using third generation pills. It is likely that none of these metabolic effects are clinically significant among healthy women.

There is a slight reduction in glucose tolerance and an increase in plasma insulin concentration in healthy non-diabetic women. The combined pill does not, however, induce diabetes. Long-term follow-up of 17 000 users has demonstrated no increase in referrals to hospital for either type 1 or type 2 diabetes.

Serious side effects involve mainly the cardiovascular system and the pill affects both the venous and arterial circulation. Arterial disease (myocardial infarction and cerebrovascular accident) is much less common but much more serious. Although the aetiology and epidemiology of venous and arterial disease differ, in both cases the increased risk appears to be related to an increased thrombotic tendency. Alterations in clotting factors creates a tendency to hypercoagulability which is partly balanced by an increase in fibrinolysis. The adverse effect on clotting is related to the dose of oestrogen and lower dose pills have been shown in some (but not all) studies to be associated with a reduced risk compared with pills containing 50 μg oestrogen.

## Venous disease

The COC increases the relative risk of venous thromboembolism (VTE) by three to six fold compared with women not taking the COC. The risk is unaffected by smoking, age or duration of pill use but is higher in obese women (BMI more than 25 kg/m$^2$) and in Europe, among women with a history of pregnancy-induced hypertension. The absolute risk of VTE attributable to COC use increases with age, obesity, recent surgery and some thrombophilias. The risk of VTE returns to normal by three months after stopping the pill.

A number of studies published in 1996 demonstrated a differential risk of VTE depending on the type of progestogen in the pill.[5] Combined pills which contained either gestodene or desogestrel were shown to have a roughly twofold increased risk of VTE when compared with pills containing first or second generation progestins. There is no evidence to suggest that progestogens have a direct effect on clotting mechanisms and the effect may result from the balance between oestrogens and the less androgenic progestins which antagonize the oestrogens less than LNG, thereby rendering third generation pills biologically more oestrogenic. It is not clear through what mechanism the risk of clot formation is increased however it has recently been demonstrated that acquired resistance to activated protein C (which downregulates *in-vitro* thrombin formation) is more pronounced during use of a pill containing desogestrel compared with one containing LNG.[6]

The findings of these studies led to widespread publicity in late 1995 and in the UK, Germany and Norway restrictions were placed on the use of pills containing gestodene or desogestrel, although in many countries no action was taken. In the UK the Committee on Safety of Medicines (CSM) recommended that COC pills containing gestodene or desogestrel should be regarded as a pill of second choice and not used by women with known risk factors for VTE. Much had been published since the original studies demonstrating a relationship between the risk of VTE and the type of progestin were published. Data were reviewed by a group of experts meeting at WHO in November 1997. The group concluded[7] that 'pills containing desogestrel and gestodene probably carry a small risk of VTE beyond that of pills containing levonorgestrel'. In 1999 the CSM removed the restrictions, advising that although the evidence was still supportive of an increased risk of VTE with pills containing desogestrel and gestodene, that women should be given the facts and allowed to choose a contraceptive pill which suited them best. Recent editorials[8,9] have advised that caution is still justified.

Although the risk of VTE is increased in women with inherited thrombophilias, widespread screening of women wishing to start using the COC is not recommended since the prevalence of thrombophilia is relatively low, the tests are complex and expensive and the large number of women who use the pill would make it an immensely costly exercise. It is however well worth screening women with a strong family history of thrombotic disease before starting combined hormonal contraception.

## Arterial disease

The WHO expert group also reviewed the data on myocardial infarction (MI) and stroke, the conclusions are a useful summary of current knowledge and were as follows.

## Acute myocardial infarction

- Acute MI is uncommon in women of reproductive age.
- The risk of MI, regardless of age, is not increased among pill users who do not smoke and do not have either hypertension or diabetes.
- Women who have hypertension and who take the COC have an increased relative risk of MI of at least three times that of women who take the COC and are normotensive.
- Smoking increases the risk of MI by 10 times when compared with COC users who do not smoke.
- There is insufficient evidence to allow any conclusion on whether the risk of MI is influenced by the type or dose of progestogen.

Thus women who have no other risk factors can be reassured that they have no increased risk of myocardial infarction. There was no increased risk of mortality due to ischaemic heart disease either during or after COC use in the report of the RCGP study.[3]

## Stroke

- Ischaemic and haemorrhagic stroke are both uncommon among women of reproductive age.
- The risk of ischaemic stroke is increased by about 1.5-fold in women who take the COC who do not smoke and are not hypertensive.
- In contrast, the risk of haemorrhagic stroke is not increased in these women until they reach the age of 35, after which the increasing natural risk of haemorrhagic stroke is magnified by COCP use.
- Hypertension increases the risk of both ischaemic (by three times) and haemorrhagic (tenfold) stroke when compared with never users.
- Smoking increases the risk of ischaemic and haemorrhagic stroke (x2-3) compared with pill users who do not smoke.
- There is insufficient evidence to determine whether the risk of either type of stroke is influenced by the type or dose of progestogen.

Thus the data are reassuring for haemorrhagic stroke, but the risk of ischaemic stroke is increased by COC use and once again this is supported by the findings of the RCGP study[3] in which the relative risk of death from stroke was significantly increased to 1.9 (confidence intervals 1.2–3.1, $p=0.009$). After ten years of stopping the pill the risk of death from stroke is no longer elevated.

Migraine is listed as one of the relative contraindications to the COC because of the association between migraine and cerebrovascular accident. The relative risk of ischaemic (but not haemorrhagic) stroke was increased among women with a personal history of migraine (RR 3.4, confidence intervals 1.30–9.61) in one large study.[10] Odds ratios were similar for classical migraine (with aura) and simple migraine (without aura). Oral contraceptive use increased the relative risk, although not statistically significantly. Pill users who have a history of

on Hormonal Factors in Breast Cancer[11] re
of 54 studies involving over 53 000 women w
100 000 control subjects. The group concluded
was associated with a small increase in breas
increased risk persisted for ten years after s
relative risk for current users was 1.24; for 1–
1.16 and for 5–9 years after stopping 1.07. Sinc
breast cancer increase with age, the effect of thi
population terms among older women whc
recently taken the COC (Fig. 1). After ten ye
breast cancer was no longer increased. Althoug
higher for women who started the pill at a you
cancer is rare in this age group) there was little
duration of use, dose or type of hormone. Sc
ever-users were significantly less likely (RR
which had spread beyond the breast even if the
more than ten years earlier. The RCGP study is
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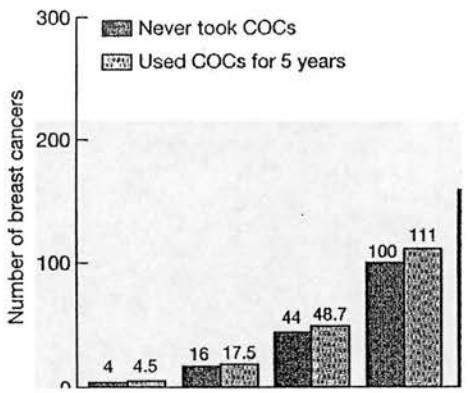
The relationship between the pill and breas
explain because the risk appears to increase soo
not increase with duration of exposure an
10 years after stopping. It has been suggested t
pill may accelerate the appearance of breast
women, that is late stage promotion of existi
possible that women using the pill have thei
earlier although it is difficult to explain why
diagnosis would persist for years after stopping
lysis, the risk of breast cancer was also increase
of both the progestogen only pill (RR 1.17) a
1.07) although the numbers of women using p
was small. Since there is no evidence that prog
with the pathogenesis of breast cancer, these fi
argument for increased detection rather than l
breast cancer. Nonetheless, a biological effect o
contraception has still not been ruled out.



## Cervical cancer

Data on the risk of cervical cancer among pill users is also difficult to interpret since barrier methods confer some protection, and the aetiology of cervical cancer is connected with sexual activity with the risk related to the number of sexual partners a woman has in her lifetime. More than five years of pill use may well be associated with an increase in the risk of squamous carcinoma of the cervix. The RCGP study reported an increased relative risk of death from cervical cancer of 2.5 (confidence interval 1.1–1.6, $p=0.04$) but this increase disappeared once women had been off the pill for more than ten years. In the UK, COC users are a captive population for cervical screening so that it should be possible to diagnose and treat malignant disease at an early stage.

Recent evidence has suggested an increased risk of adenocarcinoma among long-term users but this is a rare tumour.

## Liver cancer

Benign hepatic adenoma is a rare consequence of COC use. In countries where hepatocellular carcinoma is rare, this disease may very rarely be associated with pill use. Among populations where it is common, such as in the Far East, short-term use of the COC does not alter the incidence of hepatocellular carcinoma but data on long-term use are scarce.

## Practical prescribing

A full history should be taken to exclude risk factors which might contraindicate combined pill use or indicate the need for further investigation. Blood pressure should be measured and it may be helpful to record baseline weight. Pills containing gestodene or desogestrel are currently contraindicated for overweight women in the UK. Pelvic examination is not routinely indicated at the first visit unless there is reason to suspect gynaecological pathology. Women do not like pelvic examinations and some, particularly the young, may be deterred from starting or continuing with the method if examination is seen as a necessary prerequisite.

Cervical smears should be taken in accordance with national policy. A baseline breast examination is often recommended in new users over the age of 35 years.

New users should start with a low dose (30–35 μg) pill. If breakthrough bleeding occurs, it usually settles within the first three months but if it persists, and after excluding a gynaecological cause, a higher dose pill or one containing a different type of progestogen may be tried. Women on long-term enzyme-inducing drugs (for example, some anticonvulsants) should use a 50 μg oestrogen preparation to ensure best efficacy.

Women should be carefully instructed how to use the pill and what to do when pills are forgotten (Fig. 2). They should also be informed that some antibiotics are thought to interfere with the absorption or metabolism of the pill and thereby jeopardize efficacy. Although the evidence for this is not very convincing,[12] the advice has become standard and there is insufficient evidence to change the recommendations. Many women choose or are advised to have a break from using the pill for a few months. While cardiovascular

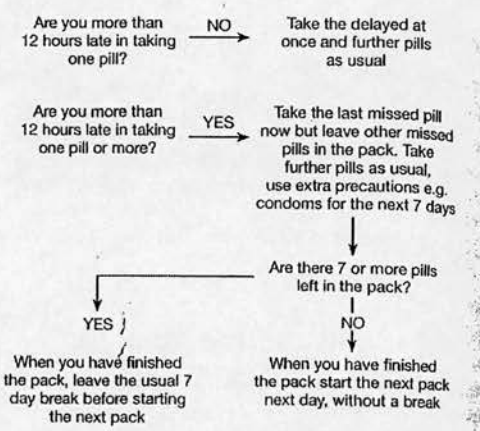



**Fig. 2** Rules for missed pills.

risks decline when the pill is stopped, they recur as soon as it is started again and unplanned pregnancies commonly occur during such breaks. Most women who stop the pill regain normal fertility within three months. Secondary, so-called post-pill amenorrhoea is almost always the result of abnormalities present before the pill was started (such as polycystic ovarian syndrome) but regular COC-induced withdrawal bleeds mask these conditions. There is no evidence of any adverse effect on the fetus as a result of previous pill use. If conception occurs during pill use the risk of teratogenesis is tiny or non-existent.

## Combined injectables

Combined oestrogen–progestogen injectable contraceptives are popular with women who like hormonal methods but forget to take pills. Cyclofem (medroxyprogesterone acetate 25 mg and oestradiol cypionate 5 mg) and Mesigyna (norethisterone enanthate 50 mg and oestradiol valerate 5 mg) are given monthly and have a very low pregnancy rate (0.5 per HWY). Vaginal bleeding occurs around every 35 days and discontinuation rates for menstrual irregularity and amenorrhoea are half those associated with progestogen only injectables. The risks and side effects are the same as for the combined pill.

## Combined contraceptive vaginal and transdermal preparations

Non-oral routes of administration of contraceptive steroids avoid the first pass through the liver allowing lower doses of hormone to be used. Constant circulating hormone concentrations may reduce the incidence of minor side effects when compared with oral administration. Most steroid hormones are well absorbed through the vaginal mucosa and soft silastic or polyethylenevinylacetate (EVA) rings have been developed which release a combination of oestrogen and progestogen and can be worn for three weeks and removed for seven days. Efficacy is as good as that of the combined pill but the user has

only to remember to insert and remove the ring once each month. A ring delivering 15 μg ethinyl oestradiol and 120 μg desogestrel[13] will become available in the USA and much of Europe in 2001.

Although transdermal preparations of oestrogen and progestogen have been available for menopausal hormone replacement therapy for some time, patches have been slow to enter the contraceptive arena. A seven day patch delivering 25 μg ethinyl oestradiol and 150 μg 17-deacetylnorgestimate underwent phase three trials[14] in 1998/1999 and should become available in 2001.

## Progestogen only contraception

Progestogen only contraception is much less commonly used than combined hormonal contraception. It is however available in a wider variety of systems including pills, implants, long-acting injectables and hormone-releasing intrauterine devices (IUDs). New delivery systems include vaginal rings, patches and a gel preparation.

The mechanism of action of progestogen-only contraceptives depends on the dose of steroid administered. High doses – for example, injectables – inhibit ovulation. Low doses inhibit ovulation only inconsistently depending on the individual response. By all routes of administration, progestogens affect both the quantity and physical characteristics of cervical mucus, reducing sperm penetrability and transport. All methods have an effect on the endometrium which probably compromises implantation.

## Advantages and disadvantages

The progestogen-only or mini pill (POP) is usually prescribed for women in whom oestrogen is absolutely or relatively contraindicated (for example, women with cardiovascular risk factors, migraine, or hypertension) and for women who are breast-feeding (since oestrogen impairs milk production). The lack of oestrogen makes progestogen only a much safer hormonal contraceptive but it also has fewer health benefits. For women who like to have amenorrhoea Depo-Provera (see below) is an attractive method of contraception which is also relatively long acting. Absence of menstruation is of benefit to women who suffer from premenstrual syndrome, menorrhagia and dysmenorrhoea and it is perhaps surprising that Depo-Provera is seldom used to manage these problems particularly in women who need contraception. Progestogen-only contraception is also said to reduce the incidence of pelvic infection, perhaps because the thickened cervical mucus prevents ascending infection. Increasingly the LNG-releasing intrauterine system (IUS) (LNG-IUS see below) is being used for the management of menorrhagia and as a means of delivering the progestogen component of hormone replacement therapy (HRT).

## Contraindications

Contraindications which apply to progestogen-only methods are shown in Box 2. In many countries regulatory authorities still insist on a long list of contraindications which apply to the combined pill but not, in reality, to progestogen-only methods such as VTE.

**Box 2 Contraindications to progestogen-only contraception**

- Absolute
  - Known or suspected pregnancy – high dose androgenic progestogens such as NET-EN may carry a very small risk of masculinization of a female fetus
  - Undiagnosed irregular vaginal bleeding
  - Any serious side effect which is not clearly oestrogen-related
  - Current history of serious cardiovascular disease
  - Injectable methods should not be used by women with a bleeding tendency – including long-term anticoagulation – because of risk of injection-site haematoma
- Relative
  - Severe obesity – the efficacy of low dose methods may be reduced and injectable may exacerbate weight gain
  - Breast cancer
  - Molar pregnancy until urine is free of hCG
  - Severe hypertension
  - History of recurrent ovarian cysts – this does not apply to injectable methods
  - Chronic liver conditions

## Risks and side effects

All low dose progestogen-only methods are associated with a high incidence of irregular vaginal bleeding. This is due in part to their effect on ovarian function. Inconsistent ovulation and fluctuating endogenous oestrogen production from irregular follicle growth causes irregular bleeding. Low dose progestogen-only methods also alter the vasculature of the endometrium perhaps increasing capillary fragility.[15]

The effect of the low dose progestogens on ovarian activity also results in a relatively high incidence of functional ovarian cysts or, more accurately, persistent follicles. Some 20 per cent of women using the POP, LNG-IUS and Norplant® or Implanon® will have one or more persistent follicles demonstrable by ultrasound. These are usually asymptomatic but can cause abdominal pain or dyspareunia. Most will disappear with menstruation and treatment should therefore be conservative.

Other side effects include headache, nausea, bloating, breast tenderness and mood change. These often settle with time. If the POP is being used, minor symptoms may sometimes be helped by changing to a different progestogen. Oily skin and acne can be a problem with the more androgenic progestogens – LNG and norethisterone. The POP is commonly said to be associated with an increased risk of ectopic pregnancy. Since the failure rate is less than 3 per cent, overall the incidence of ectopic pregnancy is in fact significantly less than that among women not using contraception.

In general, progestogens induce fewer metabolic changes than the combined pill. Effects on lipids are minimal, even with the high dose

injectable methods. Depo-Provera and NET-EN slightly increase insulin resistance but the effects are not clinically significant.

## Long-term risks

There are fewer data on the long-term risks of progestogen only contraception because the numbers of women using them are relatively small compared with the combined pill.[16] Since implants and the progestogen-releasing IUS are both relatively new, data are even more scarce and it is reasonable to extrapolate from what is known about the risks of low dose oral progestogen contraception.

## Cardiovascular disease

Since the cardiovascular risks of the combined pill are due to oestrogen it has always been felt that the risks of the POP should be negligible. This view was confirmed by the publication in 1998 of a multinational study[17] which demonstrated no statistically significant increase in the risk of acute MI, stroke or VTE among POP users or women using Depo-Provera.

## Reproductive cancers

As discussed earlier, use of the POP and Depo-Provera within the last 5 years is associated with a small increase in relative risk of breast cancer (RR 1.17 and 1.07 respectively). The increase in risk disappears 5 years after stopping and is only statistically significant for the POP. The increased risk is likely to be due to increased detection of tumours rather than to a causative relationship.

There are no data for the effect of the POP on the incidence of other reproductive cancers such as endometrial or ovarian cancer but bearing in mind the effect of low dose progestogen on the ovarian cycle there is unlikely to be a significant effect on malignant disease. Depo-Provera confers a high degree of protection against endometrial carcinoma but although it should theoretically also protect against ovarian cancer there are as yet no data to support this. There are also no data on risks of cervical cancer although it is thought that all hormonal contraception may play a very small promoting role.

## Oral progestogen-only contraception

### Available preparations

The progestogen-only or mini pill (POP) is available in daily doses of between 30 and 75 μg leading to peak concentrations of around 2.5 nmol/l. A number of different progestogens are available including LNG, norethisterone and ethynodiol diacetate (more than 90 per cent of which is converted to norethisterone as the active metabolite). As yet there are no preparations marketed containing a third generation progestogen.

Not only do these pills not contain oestrogen, but the dose of progestogen is often considerably lower than that delivered in the combined pill. A 28-day course of Microval, for example, exposes the user to a total dose of 0.84 mg of LNG compared to 3.15 mg during 21 days use of Microgynon or 5.25 mg of Ovranette. Thus the minipill is suitable not only for women with contraindications to oestrogen but also for women with conditions on which the effect of progesto on lipids may be detrimental, for example, mild hypertension.

### Mechanism of action

Around 50 per cent of women using the POP continue to ovulate a menstruate regularly. Ten per cent will experience complete suppre sion of follicular development and will have amenorrhoea. T remainder will have inconsistent ovulation, often with a short lute phase, or follicular development only or both, with the pattern ovarian activity varying from one cycle to the next. This last grou of women will experience irregular bleeding and up to 20 per cent users discontinue the POP for this reason.

### Efficacy

Since many women continue to ovulate, the POP has a higher failu rate than the combined pill (see Table 1). The POP also has a short half-life so that missing even just one pill may interfere with contra ceptive efficacy. Efficacy tends to increase with age but may b reduced by obesity and it is widely recommended that women wh weigh more than 70 kg take two tablets each day.

### Practical prescribing

For immediate effectiveness the POP should be started on the firs day of the menstrual cycle. It is taken every day and because of th shorter half-life the importance of taking the pill at the same time each day should be emphasized. If the POP is taken more than 3 h late, the rules for missed COC pills should be followed. Similarly it has become widespread practice to recommend secondary protection (with a barrier method) in the presence of concurrent antibiotic use or gastro-intestinal upset.

It is not possible to predict the pattern of ovarian activity (and therefore the bleeding pattern) that an individual woman might expect. If irregular and frequent bleeding is a problem an alternative method of contraception should be discussed since bleeding patterns do not improve with time and nor is the problem relieved by trying a different progestogen.

Once the POP is stopped normal fertility resumes within days.

## Injectable progestogen-only methods

### Available preparations

Long-acting injections of norethisterone-enanthate (NET-EN) and medroxyprogesterone acetate (DMPA, Depo-Provera) are both highly effective methods of contraception. NET-EN is rarely used in the UK as the preparation has to be warmed before it can be drawn up into a syringe and it is administered every 8 weeks (at least initially) as compared with 12 weeks for DMPA (Depo-Provera).

Depo-Provera is given by intramuscular injection, 150 mg every 12 weeks.

### Side effects

The high dose of progestogen inhibits ovulation and by the end of one year of use 80 per cent of women have either infrequent scanty

vaginal bleeding or amenorrhoea. Heavy prolonged bleeding may be a problem in around 2 per cent of women. The cause is unknown and often leads to discontinuation of the method. Bleeding can be temporarily alleviated by the administration of oestrogens (the easiest way is to give the combined pill), but it often persists for some months after Depo-Provera is stopped.

It may take up to one year for normal fertility to return following cessation of Depo-Provera. Women often complain of 'feeling premenstrual' despite continuing amenorrhoea. They can be assured that there is no permanent impairment of fertility but this delay makes Depo-Provera an inappropriate method for women wishing short-term contraception.

Many women wrongly attribute weight gain to the use of hormonal contraception. Depo-Provera however is associated with weight gain and women may gain as much as 16 kg after two years of use.

Complete inhibition of ovulation by Depo-Provera is associated with hypo-oestrogenism and amenorrhoea. Hypo-oestrogenism is associated with a reduction in bone mineral density. Two papers published in the early 1990s showed that long-term use of DMPA resulted in BMD loss[18] which partially recovered after stopping the method.[19]

In response to the concerns raised, a variety of suggestions were made as to how to manage women on long-term DMPA including the addition of 'add-back' oestrogen (for example, an HRT patch). However many women who use DMPA have contraindications to oestrogen and it adds considerably to the cost and complexity of the method. Reassuring data have been published recently. A cross sectional study[20] from the UK of 185 women using Depo-Provera for more than five years or amenorrhoeic after one year of use, showed only a minimal change in BMD which was thought unlikely to be of clinical significance. Similarly no significant difference in BMD is demonstrable when past-users are compared with controls.[21] Concerns remain however about the use of DMPA in adolescents who have yet to achieve their peak bone mass. The effect of hormonal contraception on bone mass is reviewed in a useful article by Meirik (2000).[22]

### Practical prescribing

For maximum efficacy DMPA should be given in the first five days of the menstrual cycle.

## Progestogen-only implants

The first contraceptive implant to become available in the UK was the six capsule implant Norplant® which became available in 1993. Marketing of Norplant in the UK ceased in 1999 for a number of reasons but mainly probably because of the introduction of a single rod implant Implanon®.

### Norplant®

Norplant® is a long-acting hormonal method of contraception consisting of six flexible capsules releasing a low dose of LNG (30–35 μg/24 h after 18 months). The capsules are inserted subdermally in the inner aspect of the upper arm under local anaesthesia. Insertion and removal are minor surgical procedures which require specialized training. Although no longer available in the UK Norplant has been used by some 60 million women worldwide and is registered in over 60 countries.[23] An implant which uses only two rods (Norplant 2 or Jadelle) is now licensed in some countries.

Norplant is highly effective (Table 1). It is marketed as a method which lasts for five years but there are good data demonstrating efficacy for more than seven years.

### Implanon®

Implanon® is a single rod, 4 mm long and 2 mm in diameter, containing approximately 68 mg etonogestrel within a EVA membrane.[24,25] Each rod comes individually packed in a sterile disposable inserter (Fig. 3). Daily release rates are around 67 μg and fall only very slowly during the life of the implant which is three years. The dose of progestogen is sufficient to inhibit ovulation in all users for the duration of treatment and this is reflected in both the efficacy and bleeding patterns. In trials totalling almost 3000 women years of use, to date there have been no pregnancies reported during the use of Implanon.[26] Since ovulation is inhibited in almost every user throughout the three years of use amenorrhoea is slightly more common among women using Implanon, (21 per cent during any three-month reference period) compared with women using Norplant or Jadelle.

### Side effects

Minor side effects include weight gain, headache, mood change and acne. As with all low dose progestogen-only methods menstrual disturbance is the most frequently reported side-effect, and occurs in nearly all users with many bleeding irregularly and unpredictably through three years. Heavy bleeding is uncommon. Many women do not like the unpredictability of bleeding, and even very light bleeding is unacceptable if it lasts for days on end. Long-term use is essential for cost effectiveness, and careful counselling, particularly about menstrual irregularities, is vital to avoid premature discontinuation. Menstrual change accounts for the great majority of discontinuations.

As with the POP, ovarian enlargement due to persistent unruptured follicles has been noted in some women. The follicles can reach 5–7 cm in diameter but usually regress within 1–2 months. They may be accompanied by mastalgia and abdominal pain and management should be conservative.

Most studies demonstrate a slight reduction in circulating triglycerides, total cholesterol and LDL concentrations with only a minimal effect on HDL. No clinically significant changes in clotting factors have been described and it is likely that the effects of progestogen-only

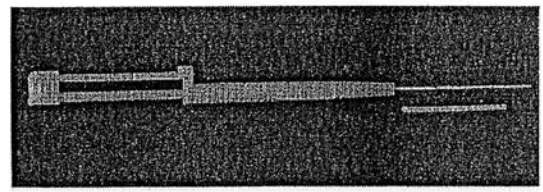


**Fig. 3** Implanon and its disposable inserter.

implants on the risks of cardiovascular disease are no different from those described for the progestogen-only pill.

Long-term (five years) follow-up of over 16 000 women using Norplant shows no significant excess of any health problems including ectopic pregnancy, cardiovascular disease and neoplasia.[27] Such long-term safety data are not yet available for Implanon but it seems unlikely that they would be different. Normal ovulatory cycles return rapidly after removal of both Implanon and Norplant and conception rates and the outcome of pregnancy following Norplant removal is no different from that following the use of any other hormonal method of contraception. As yet there are no data for Implanon.

## Progestogen-releasing intrauterine system

Hormone releasing IUDs were developed in the 1970s but it was not until 1995 that a LNG-releasing device (Mirena) became available in the UK. Marketed as an intrauterine system (LNG-IUS) to distinguish it from non-medicated devices the LNG-IUS has a sleeve of LNG (52 mg) around its stem (Fig. 4) releasing 20 μg LNG per day and lasting for at least 5 years.[28] In the USA an IUS which releases 65 μg progesterone a day is available. This system is licensed for only one year.

### Mechanism of action

Copper-containing IUDs are thought to have a toxic effect on gametes (both sperm and eggs) thereby reducing the chance of successful fertilization. They also stimulate an inflammatory reaction in the endometrium which will inhibit implantation.[29] The LNG-IUS probably acts similarly but in addition causes endometrial atrophy. The dose of LNG is too low to inhibit ovulation in most women.

### Efficacy

The LNG-IUS is more effective than a copper IUD (Table 1) presumably because of the additional effects on cervical mucus characteristics and on endometrial atrophy.

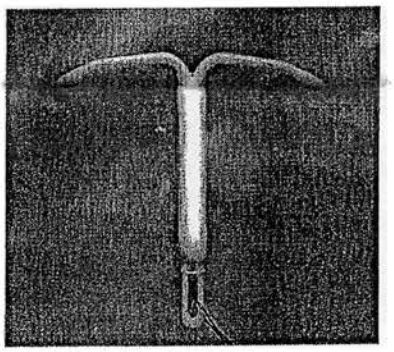


**Fig. 4** Mirena – the levonorgestrel-releasing intrauterine system.

### Advantages

Intrauterine devices are long acting methods of contraception which, once inserted, can be forgotten about. Copper devices are extremely cheap. The cost of the LNG-IUS is comparable with the COC if it is used for five years.

Copper IUDs increase the duration and quantity of menstrual bleeding in many women and 20 per cent of them will stop using an IUD because of menorrhagia. In contrast the LNG-IUS decreases blood flow by causing endometrial atrophy. The LNG-IUS is licensed in Scandinavia, and in the UK, for the treatment of menorrhagia. Andersson and Rybo (1990) demonstrated that after one year of use median blood loss fell to 10 ml among 19 women with menorrhagia.[30]

The LNG-IUS is said to reduce the risk of pelvic infection perhaps because the progestogen causes thickening of the cervical mucus impeding the passage of infectious agents into the uterine cavity. In reality the risk of pelvic infection with all IUDs has been overemphasized and in women whose lifestyles do not put them at increased risk of sexually transmitted infections, the risk is minimal.

In addition to its use as a contraceptive, the LNG-IUS is now licensed (and widely recommended) for the medical management of menorrhagia[31] and the system may also be of value as a route of administration for the progestogen component of postmenopausal HRT. Many women find the side effects of progestogens unpleasant and progestogens are only required to oppose the neoplastic effects of oestrogen on the endometrium. A very low dose of progestogen with local effects on the endometrium but few systemic side effects would be preferred by many women.

### Risks and side effects

The risk of perforation of the uterus (less than 1 per cent) at the time of insertion of the LNG-IUS and of expulsion (less than 5 per cent) is probably less than that for copper IUDs because the device is larger.

Many women find that menstrual periods are replaced by prolonged light vaginal spotting which may or may not improve with time. Women who have menorrhagia find this quite acceptable, but women who do not have menstrual dysfunction are often dissatisfied with this pattern of bleeding.

There are as yet no data on the long term safety of the LNG-IUS. In theory the risks of cardiovascular disease and neoplasia should be no different from those of other low dose progestogen contraceptives. The risk of endometrial cancer may be reduced but it will take years before there are data to support this hypothesis.

### Practical prescribing

The LNG-IUS is a relatively large device which may be difficult to insert in a nulliparous women or in an atrophic uterus following, for example, prolonged use of the COC or Depo-Provera. Insertion may be helped by the use of local anaesthesia or by pre-treatment with either oral or vaginal misoprostol which has been shown to dilate the non-pregnant cervix.[32] Insertion should take place during the first five days of the menstrual cycle and the IUS can be removed at any time if pregnancy is desired. Women should be warned to expect irregular vaginal spotting at least during the first three months of use and perhaps for longer. Ten per cent of women will develop amenorrhoea. Normal fertility resumes within 48 h of removal of the IUS.

## Vaginal rings

Progestogen-only vaginal rings have been in development for some time but are as yet not licensed in any country. Using doses equivalent to those of the POP, side effects, particularly bleeding patterns, and efficacy are likely to be similar. The advantage will be in terms of compliance since it is likely that rings can be designed to last for at least four months and can simply be inserted into the vagina and forgotten about.

## Patches and gels

The Population Council (New York) is presently developing patches and gels for the transdermal administration of a non-androgenic progestogen – Nestorone – which is inactive by the oral route.

## Emergency contraception

Emergency contraception can be defined as any drug or device which will prevent pregnancy after intercourse has taken place. Emergency contraception is useful after unprotected intercourse or withdrawal which occurs too late and for couples who experience and recognize a failure of a barrier method such as a burst condom. It is not usually recommended when oral contraceptive pills have been forgotten since there are established rules for use of a barrier method as secondary prevention under these circumstances (Fig. 2).

It has been calculated that the widespread use of emergency contraception could prevent substantial numbers of unintended pregnancies.[33] The first method to be described was high dose oestrogen but this approach has largely been abandoned because of a high incidence of nausea and vomiting. From 1984 until 1999 the most widely used hormonal emergency contraceptive – and the only method licensed in the UK – was a combination of ethinyl oestradiol and LNG (Schering PC4). In 2000 following a randomized controlled trial by WHO[34] demonstrating similar or superior efficacy and a much better side effect profile, LNG alone was licensed for emergency contraception in the UK, USA and much of Europe. More effective but much less convenient to use, the intrauterine contraceptive device prevents up to 99 per cent of pregnancies if used post-coitally.

### Combined oestrogen–progestogen

Schering PC4 is a combination of 100 μg ethinyl oestradiol and 0.5 mg LNG taken twice with the two doses separated by 12 h. The regimen is recommended for use within 72 h after intercourse. The same hormones are available in some brands of combined oral contraceptive pills. It is not known whether COCs containing other progestins administered in a similar manner are effective.

### Progestogen only emergency contraception

Progestogen alone is an effective post coital agent. Marketed by Schering Healthcare as Levonelle-2 it comprises 0.75 mg LNG given twice with the two doses separated by 12 h and the first dose given within 72 h of intercourse.

Recent data suggest that both PC4 and LNG alone may be much more effective if taken within 24 h and that efficacy falls with time.[35]

### Mechanism of action

There is good evidence that Schering PC4[36] and LNG alone[37] inhibit or delay ovulation in some women some of the time. Unfortunately they are both probably less likely to do so when a mature follicle is present in the ovary (and therefore when the risk of pregnancy is greatest). Although it has been suggested that Schering PC4 may inhibit implantation the data are difficult to interpret and not very convincing. Recent research[38] has been unable to demonstrate any effect of levonorgestrel on the endometrium and it is possible that either hormonal EC does not work, or works much less well, if it is used after ovulation has occurred. Since the inconsistent disruption of ovulation seems insufficient to explain the apparent efficacy of either Schering PC4 or LNG alone it is possible that other mechanisms of action (such as the inhibition of sperm transport) may be involved.[39]

### Efficacy

The exact efficacy of emergency contraception is difficult to calculate. Most studies include large numbers of young women of unproven fertility; neither the timing of intercourse nor the date of the last menstrual period are always accurately recalled; the day of ovulation may vary by as much as two or three days each cycle for any individual woman; users are not always honest or accurate about the number of acts of intercourse that have occurred and unprotected intercourse often occurs again after emergency contraception has been used. Using known estimates of the probability of pregnancy on different days of the cycle, it is possible to compare the number of pregnancies that actually occur with the number expected. In this way it has been calculated that Schering PC4 is between 70 and 80 per cent effective[40] however the WHO trial[34] comparing the two methods (using an intention to treat approach to the analysis of efficacy) suggested that Schering PC4 prevented less than 60 per cent of pregnancies while LNG alone prevented over 85 per cent.

### Risks and side effects

Nausea (up to 50 per cent) and vomiting (up to 20 per cent) are the main side effects of Schering PC4. Both may interfere with compliance, and vomiting may reduce efficacy if it occurs soon enough to interfere with absorption of the contraceptive steroids. Levonorgestrel alone is associated with a much lower incidence of nausea and vomiting and for this reason has become the method of choice. With both methods, subsequent menses normally occurs at the expected time. There are few data on the safety of the CEP regimen and none for LNG alone. Although the dose of ethinyl oestradiol in PC4 is relatively high compared with that in the COC the exposure is short. Nevertheless many doctors make no distinction between the known risks of the combined pill and the theoretical risks of emergency contraception. They worry particularly about venous thrombosis. A recent case control study demonstrated no increase in the risk of VTE.[41] Levonorgestrel, as discussed above, has been used for many years in a variety of long-acting methods of

contraception which are extremely safe. It is unlikely that LNG used as an EC will have any health risks and since it contains no oestrogen there are no concerns about VTE. It is probably mainly for this reason that Levonelle has, after much lobbying by the medical profession, become available off prescription in the UK. Unfortunately at £20 it is expensive.

## Practical prescribing

Hormonal emergency contraception is safe. There are really no contraindications to its use and the contraindications to the pill certainly do not apply. When prescribed by a doctor it is common to take a careful medical history and check the blood pressure. Since it will not work if a woman is already pregnant, it is as well to exclude pregnancy by asking about the date (and normality) of the last menstrual period. It is not necessary to do a pregnancy test or a pelvic examination unless there is clinical suspicion of pregnancy or pathology. If there has been more than one act of unprotected intercourse in that cycle pregnancy may have already occurred but emergency contraception should not be denied as there is no evidence of teratogenesis. It is perfectly safe to use emergency contraception as often as it is required. Since it is only 75–85 per cent effective it is not sensible, however, to use it as a regular method of contraception.

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## 8.1.3 Premenstrual syndrome

*Inger Sundström and Torbjörn Bäckström*

### Introduction

Premenstrual syndrome (PMS) or premenstrual dysphoric disorder (PMDD) is a psychoneuroendocrine disorder. Fluctuations in gonadal hormones, psychiatric vulnerability traits and psychosocial factors act in concert to provoke symptoms in affected women during the luteal phase of the menstrual cycle. To be able to get a full understanding of PMS one has to integrate knowledge from several clinical disciplines including the endocrine, neuroendocrine, psychiatric, and psychosocial fields. This review will emphasize aspects gathered from research in the gynaecological endocrinology and psychiatry fields.

There is great confusion, and sometimes controversy, among women and clinicians about what PMS is and what to call it. This is largely due to the failure to appreciate that although most women experience mild mood and somatic symptoms premenstrually, a small but significant number is severely disabled by the disorder. Furthermore, scientists in the field of PMS have not agreed on which terminology to use. The terms PMS and PMDD are used interchangeably by some researchers. Others claim that there is a distinction between PMS and PMDD, where the term PMS should be reserved for milder somatic symptoms such as breast tenderness, bloating, headache, and minor mood changes. However, this presentation will adhere to the term PMS, as it is more familiar among gynaecologists. Whenever the term PMS is used in this chapter, the definition will be according to the criteria stated by the American Psychiatric Association's Diagnostic and Statistical Manual of Mental Disorders, 4th edition[1] (DSM-IV) for PMDD.

PMS is a commonly encountered disorder in the western world and has a substantial impact on several aspects of the daily lives of women. The disorder is defined by the cyclical recurrence of a cluster of negative mood symptoms and physical symptoms. Symptoms develop in the luteal phase of the menstrual cycle and remit within a few days after the onset of menstrual bleeding. DSM-IV defines diagnostic criteria for PMDD, Box 1. To fulfil the criteria for PMS (or PMDD) a patient needs to present with at least five of the listed symptoms during the premenstrual week. At least one of these symptoms must be a mood symptom such as depressed mood, anxiety, affective lability or irritability. Other symptoms described

**Box 1 Summary of PMS criteria**

- (A) In most menstrual cycles during the past year, five (or more) of the following symptoms were present for most of the time during the last week of the luteal phase, began to remit within a few days after the onset of the follicular phase and were absent in the week postmenses with at least one of the symptoms being either (1), (2), (3) or (4).
  - (1) Markedly depressed mood, feelings of hopelessness or self-deprecating thoughts;
  - (2) Marked anxiety, tension, feelings of being 'keyed up' or 'on edge';
  - (3) Marked affective lability;
  - (4) Persistant and marked anger or irritability or increased interpersonal conflicts;
  - (5) Decreased interest in usual activities;
  - (6) Difficulty in concentrating;
  - (7) Easy fatigability or marked lack of energy;
  - (8) Marked change in appetite, overeating or specific food cravings;
  - (9) Hypersomnia or insomnia;
  - (10) Sense of being overwhelmed or out of control;
  - (11) Other physical symptoms, for example, breast tenderness or swelling, headaches, joint or muscle pain, a sensation of 'bloating', weight gain.
- (B) Symptoms must interfere with work, school, usual activities or relationships with others.
- (C) Symptoms must not merely be an exacerbation of another disorder, such as major depressive disorder, panic disorder, dysthymic disorder or a personality disorder.
- (D) Criteria (A), (B) and (C) must be confirmed by prospective daily ratings for at least two cycles.

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# New developments in contraceptive drugs for use by women

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Since the oral contraceptive pill was first marketed in 1959, advances in contraceptive drugs for women have been limited to variations on the theme of oestrogen in combination with progestogen or progestogen alone. Alterations to the pill regimen, new progestogens and new delivery systems have increased choice but while these advances significantly improve acceptability, side effects and risks remain essentially unchanged. New ideas are in short supply. Antiprogesterones offer a new approach with a variety of dose regimens but their development has been seriously hampered by the politics associated with their abortifacient action. Other hormone antagonists as contraceptives seem a long way off. Immunocontraception is still at a very early stage. Genes, whose products are uniquely concerned with reproductive processes, promise new targets but radically new contraceptive drugs for women appear distant.

Keywords: antihormones, contraception, oestrogen, progestogen, women

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## 1. Introduction

Throughout time, mankind has taken steps to limit family size. Although the male condom has been around for thousands of years, modern contraception for use by women dates only from the 1900s when the intrauterine device (IUD) and cervical cap were developed. The combined oral contraceptive pill (COC) came onto the market in 1959, heralding the start of the so-called contraceptive revolution.

In the last four decades, advances in contraceptive drugs have been limited to hormonal methods and specifically to variations on the two themes of oestrogen in combination with progestogen or progestogen alone. The HIV/AIDS epidemic stimulated research to improve barrier methods of contraception. Differently shaped male condoms made of different materials, condoms for women and modifications to the design of the diaphragm have almost exhausted the limited potential of barrier methods for new developments. Much of the research effort in this area is now concentrated on the development of vaginal microbicides (with or without inherent spermicidal activity and alone or in combination with existing spermicides) which will protect against sexually transmitted infections, particularly HIV.

The IUD too has limited scope for improvement. Copper was added to the inert frame of the IUD in the late 1960s allowing production of a smaller device. Most clinicians (the author of this article included) and certainly most women, do not regard copper IUDs as drugs; however, recent advances have focused on its use as a delivery system for hormones. Other compounds, such as antihormones and inhibitors of angiogenesis, represent more exciting potential candidates for intrauterine delivery.

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In some developing countries, 'medical methods' of inducing sterilisation for both women (e.g. using quinacrine [1]) and men (e.g. using a preparation of styrene maleic anhydride dissolved in dimethyl sulphoxide [2]) are used. These advances have not been considered in this review.

During the two decades following the launch of the pill, a number of pharmaceutical companies were involved in contraceptive research. Simultaneously, not-for-profit organisations such as the Population Council and WHO were actively working on the development of new methods with the needs of the developing world predominantly in mind. Since 1980, the interest of pharmaceutical companies in contraceptive development has waned [3] for a number of reasons including:

- the high cost of developing new products
- the cost of product liability, particularly in the US
- stringent regulatory requirements with a long and expensive registration process and a concomitant decrease in patent protection
- a dearth of ideas for fundamentally new products
- a hostile political climate, particularly in the US
- competition from the public sector through the provision of free or low-priced contraceptives in developing countries
- high contraceptive prevalence in developed countries where pharmaceutical companies make most of their profit

Very recently, even the interest of the not-for-profit organisations has dwindled. This is in part due to the commonly held view that, in the face of the HIV/AIDS epidemic, it borders on unethical to think of developing new contraceptives which do not simultaneously protect against HIV.

## 2. Mechanism of action of contraception for women

The control of reproduction in the female is a complex process which is incompletely understood. Gonadotropin-releasing hormone (GnRH) from the hypothalamus stimulates the secretion of luteinising hormone (LH) and follicle-stimulating hormone (FSH) from the anterior pituitary. Stimulation of the ovary by FSH encourages the development, at the start of each menstrual cycle, of around 20 follicles. In most cycles only one follicle reaches maturity, the rest become atretic. In response to rising levels of oestrogen production from the dominant follicle, a midcycle surge of LH stimulates ovulation, releasing the mature egg from the ovary. If sperm are present, fertilisation usually occurs in the fallopian tube and the fertilised egg implants in the endometrium, ~ 6 – 8 days after ovulation. Although the start of pregnancy may be defined as occurring at any point in this process, in the Western world most clinicians, scientists and the law, define pregnancy as beginning when implantation occurs.

The interruption of female fertility can potentially be achieved by interfering with any one (or more) of these processes. Inhibition of ovarian function may be either partial or complete. The COC, for example, inhibits both follicular development and ovulation so there is no egg to be fertilised. The drawback of this approach is that it is ovulation, followed by 14 days of progesterone secretion which, unless conception occurs, determines regular menstruation. In the belief that it would seem more natural and therefore improve acceptability, the combined pill was designed in such a way that regular menses is induced by a seven-day, pill-free interval causing oestrogen withdrawal bleeding [4]. If ovarian activity is completely inhibited, by for example the high dose of progestogen in depot medroxy-progesterone acetate (Depo Provera®), amenorrhoea will result. If, however, ovulation is inhibited but follicular development maintained, irregular bleeding will result from the effect on the endometrium of fluctuating levels of oestrogen coming from follicles which develop to an immature stage and then become atretic. Low-dose progestogen-only methods of contraception (oral pills and implants) inhibit folliculogenesis and ovulation only inconsistently in most women and are associated with irregular unpredictable bleeding.

Conception may also be prevented by inhibiting fertilisation. There are no contraceptive drugs which are expressly designed to prevent fertilisation and will not be until we have a clear understanding of the normal physiological processes involved.

Alterations in tubal motility or in the tubal environment, which either delay the passage of gametes or interfere with the conditions required for fertilisation, present a possible approach to new contraceptives but have the theoretical risk of inducing ectopic pregnancy.

Preventing implantation by interfering directly with the development of a receptive endometrium is probably part of the mode of action of the IUD and perhaps of low-dose progestogen-only methods. Implantation can also be disrupted by interfering with progesterone production from the corpus luteum, although if this is done after implantation has been completed it is theoretically the induction of abortion.

## 3. Steroid hormone contraception

### 3.1 Combined oral contraception

Through the last two decades research in hormonal contraception for women has centred on four specific areas; altering the 21 plus 7 day regimen, phased pill regimens, developing new progestogens with a better side effect profile, and exploring new routes of administration for hormone delivery.

#### *3.1.1 Altering the 21 plus 7 day regimen*

When the pill was first marketed in 1959, the dose of oestrogen was 150 µg/day [4]. When the increased risk of venous thromboembolism (VTE) was recognised, the dose was reduced to 50 µg and then to the so-called low-dose 30 µg pill that is in use today. Pills containing 20 µg of ethinyl oestradiol (EE) are probably approaching the threshold of efficacy and are certainly associated with slightly reduced cycle control (i.e., with more irregular/unscheduled bleeding) [5]. Keen to

reduce the dose of EE still further but anxious about compromising efficacy, the pharmaceutical industry has fixed its attention on the pill-free interval (PFI). The classical 7-day interval is sufficient to allow the resumption of follicle development in many women. Ultrasonography demonstrates the presence of follicles of ≥ 10 mm in diameter at the end of the PFI, some of which have the potential to mature and ovulate if the start of the next packet of pills is delayed [6]. It is possible simply to shorten the PFI and market a pill for say 23 + 5 days. A comparison between a pill containing 20 µg EE in combination with 75 µg gestodene and given for 23 days followed by a 5-day PFI, with a 21 + 7 day 20 µg EE pill regimen comprising150 µg desogestrel showed no difference in pregnancy rates or cycle control but was associated with withdrawal bleeds of shorter duration [7]. It is likely that the sample size of study necessary to demonstrate a significant difference in efficacy would be prohibitive. Using a 24 + 4 day pill regimen, a preparation containing 15 µg EE plus 60 µg gestodene (Schering AG, Berlin, Germany) has undergone Phase III trials in Europe [8]. Contraceptive efficacy appears similar to that of 30 µg COCs, with a Pearl Index of 0.2. In a recent study designed to investigate cycle control with this product, involving 58 women using the pill for one year, irregular bleeding occurred in 19% of cycles – higher than that typical of higher dose pills [9]. Despite the very low dose of oestrogen, no differences in coagulation markers compared with higher dose pills could be identified.

A more imaginative solution is to stop the oestrogen/progestogen combination regimen, inducing a withdrawal bleed, but to include 4 – 5 days of low-dose EE to maintain the suppression of follicle growth, with a PFI of only two days. A pill containing 150 µg desogestrel and 20 µg EE given for 21 days is followed by two days of placebo and then five days EE 10 µg/day (Mircette™,Organon, West Orange, NJ, USA) is now marketed in the US but not yet in the UK. The Pearl index among 1143 women over 18 months of use was 1.02/100 women years [10]. In a randomised study involving 47 women this regimen suppressed follicular development (as measured by ultrasound) more effectively than a regimen with the standard 7-day PFI [11].

The pill-free interval can simply be removed altogether. Its only purpose is to confer a regular withdrawal bleed but it provides opportunities for errors of compliance and probably accounts for many pregnancies attributed to pill failure. In Europe for many years, women have run packets of pills together intentionally to avoid a withdrawal bleed either purely for convenience or to reduce menstrual side effects like dysmenorrhoea or premenstrual symptoms [12]. The concept was first described in the literature in the mid 1970s [13]. In a recent study of 90 women randomised to a 21 + 7 day or a 42 + 7 day pill cycle for one year, 52.4% of women assigned to the 49 day cycle elected to continue the extended regimen when the study was finished [14]. Of the women assigned to the 28-day cycle, 16.7% also adopted extended cycles of pill use. It is only very recently that the industry has considered markering a trimonthly combined oral contraceptive pill. A monophasic pill containing EE in combination with levonorgestrel (LNG) as 84 + 7 days in a single pack (Seasonale, Barr Laboratories, USA) is currently under trial in the US [15].

### 3.1.2 Phased pill regimens

The total dose of hormone administered can be altered slightly by using biphasic or triphasic regimens in which the dose of steroids changes twice or three times during the 21 days of pill administration. Despite there being no evidence that either cycle control or side effect profiles are any better than with monophasic pills, it seems that there is still an interest in this approach. A recent publication described a new pill regimen (Estrostep™) in which the dose of progestogen remains constant (norethindrone 1 mg/day) but the dose of EE changes (20 µg/day for 5 days, 30 µg for 7 days and 35 µg for 9 days) [16]. The intention is to reduce the androgenic impact of the progestogen by giving a little more (but not much more!) oestrogen. Increased circulating sex hormone binding globulin (SHBG) and decreased testosterone concentrations suggest 'little if any intrinsic androgen activity' but side effects have not been evaluated in large studies.

### 3.1.3 New progestogens

The progestogens most commonly used in contraceptives (norethindrone, LNG, 3-keto-desogestrel, gestodene and norgestimate) are derived from 19-nortestosterone, bind to androgen receptors and are said to be associated with 'androgenic side effects'. Acne is indisputably one such side effect. Others, such as loss of libido, weight gain and changes in lipid profiles and mood, are often attributed to the androgenic properties of the progestogen but in reality the relationship is less clear. The search for less androgenic progestogens has occupied the industry for many years. Gestodene and desogestrel (the so-called third generation progestogens), when not in combination with oestrogen, certainly have a lower binding affinity for androgen receptors than LNG. In the COC, however, any clinically relevant androgenic effects are often overcome by oestrogen. All combined pills for example tend to improve acne and it is likely that only a pill containing a specific anti-androgen (such as cyproterone acetate) is significantly superior. Undeterred it would seem by the pill scare of 1995 in which the apparent increased risk of VTE associated with desogestrel and gestodene has been attributed by some to their less androgenic (and thereby more oestrogenic) profiles [17], the search for less androgenic progestogens continues.

#### 3.1.3.1 Nestorone

Nestorone (16-methylene-17α-acetoxy-19-norpregn-4-ene-3,20-diene, [NES]), formerly known as ST1435, is a potent 19-nor-progesterone derivative which is not active orally. It has strong progestational activity but lacks androgenic, oestrogenic or glucocorticoic activity [18]. In steroid receptor binding studies, 3-keto-desogestrel showed the highest binding affinity to progesterone receptors (PR) followed by nestorone,

LNG and progesterone. The binding affinity of nestorone to androgen receptors (AR) was 500 – 600-fold less than that of testosterone and much less than that of LNG or 3-keto-desogestrel. None of the progestogens bound to the oestrogen receptor (ER). Despite significant binding to glucocorticoid receptors, nestorone showed no glucocorticoid activity *in vivo* in adrenalectomised rats.

Concluding that the high progestational potency and lack of androgenic, oestrogenic and glucocorticoid activity confers special advantages to nestorone for use in contraception (and in hormone replacement therapy [HRT]) the Population Council (New York, USA) has been exploring its potential in long acting contraceptive delivery systems including implants and vaginal rings (see section 3.3).

*3.1.3.2 Drospirenone*

Drospirenone is a progestogen derived from 17α-spironolactone. Receptor binding studies demonstrate progestogenic potency similar to progesterone but no androgenic, oestrogenic, glucocorticoid and antiglucocorticoid activity [19]. Drospirenone however has anti-androgenic activity and, in contrast to all other progestogens currently used in contraception, antimineralocorticoid properties. Drospirenone 2 mg alone orally for 6 days resulted in a cumulative sodium loss of 84 mmol and a significant rise in plasma renin and aldosterone compared with placebo [20]. From cycle days 5 – 25, 2 mg of drospirenone suppressed ovulation and resulted in a slight natiuresis with no change in blood pressure [18]. Drospirenone 3 mg/day in combination with 30 µg EE has recently been marketed in Europe (Schering AG) and the US (Berlex Laboratories, Montville, NJ) as the combined oral contraceptive pill, Yasmin™. Its main selling point is the associated reduction in fluid retention (due to the antimineralocorticoid effect) leading to weight loss or at least less weight gain when compared with a pill containing desogestrel [21]. The difference in weight is small and it is possible that the anti-androgenic effect may be associated with a marginally increased risk of VTE (demonstrated with pills containing cyproterone acetate [22]), perhaps made worse by a slight fluid depleted state.

*3.1.3.3 Nomegestrol acetate*

Nomegestrol acetate {pregna-nor-4,6diene-3,20-dione 6-methyl-17β-acetoxy-19-) is an orally-active 19-nor-progesterone-derived progestogen which has been around for some time and which is currently used in HRT preparations in Europe [23]. Doses of 1.25 mg/day inhibit ovulation in women without inhibiting follicular maturation perhaps by disrupting the positive feedback-induced LH surge [24]. It has been developed as a contraceptive implant (see section 3.3) and Phase II studies of an oral pill are underway (Merck-Theramex).

*3.1.3.4 Trimegestone*

Trimegestone (TMG; 17b-[(S)-2-hydroxypropanoly]-17-methyl-estra-4,9-dien-3-one) is a 19-norpregnane progestin under development for HRT and oral contraception (co-developed by Hoechst Marion Roussel and Wyeth-Ayerst). It has a better receptor selectivity profile than medroxyprogesterone acetate (MPA) in rat and rabbit models and possess weak anti-androgenic activity without androgenicity [25].

## 3.2 Oral progestogen-only contraception

Oral progestogen-only contraception has been available for decades but is used by only a small number of women worldwide. It accounts for ~ 2% of the hormonal contraception market in the UK and is used mainly by women who have contraindications to oestrogen, particularly breastfeeding. Until recently, no new progestogen-only pills (POP) have been developed.

### *3.2.1 Desogestrel-only pill*

A POP containing 75 µg desogestrel is currently marketed in some European countries, but not yet in the UK or the US, by NV Organon (Oss, The Netherlands). This dose inhibits ovulation much more consistently than other currently available POPs which rely on the effect on cervical mucus for their contraceptive efficacy. In a head-to-head comparison with 30 µg LNG, desogestrel 75 µg among 64 women randomised to the method for one year, follicular rupture (confirmed by ultrasound) occurred in 36% of cycles in the twelfth treatment period among users of LNG but in only 3% of cycles among users of desogestrel [26].

## 3.3 New hormone delivery systems

Avoidance of the oral route of administration for contraceptive steroids has the advantage of bypassing the first phase of metabolism through the liver. This allows the dose of hormone to be reduced thereby theoretically improving safety. Non-oral delivery systems also have the potential to deliver very constant amounts of drug, theoretically reducing side effects which are sometimes attributed (perhaps naively) to daily fluctuations in steroid dose. Most importantly, the new delivery systems provide long-acting contraceptives which depend less, or not at all, on compliance for their effectiveness.

### *3.3.1 Contraceptive implants*

Several implants have been developed for female contraception [27]. Inserted subdermally, under local anaesthesia in the inner aspect of the non-dominant arm, they begin to release the progestogen immediately following insertion. The amount of steroid released drops slowly and progressively with time. Their effective lives extend from 6 to 84 months.

*3.3.1.1 Jadelle*

A two rod levonorgestrel implant (Jadelle®) achieves virtually the same performance as Norplant® but fewer rods allows easier insertion and removal. Each rod consists of 75 mg of LNG crystals embedded in a dimethylsiloxane/methylvinylsiloxane copolymer [28]. LNG serum concentrations fall rapidly from 770 pg/ml to half this value during the first month after insertion. Thereafter serum concentrations decline slowly to ~ 275 pg/ml at the end of three years. Effectiveness, side effects,

continuation rates and return to fertility after removal are not clinically different from those associated with Norplant.

*3.3.1.2 Implanon*

Implanon™ (NV Organon Oss, The Netherlands) is a single unit implant releasing etonogestrel (ENG, 13β-ethyl-17β-hydroxy-11-methylene-18,19-dinor-17α-pregn-4-en-20-yn-3-one), the biologically active metabolite of desogestrel. The steroid crystals are embedded in a rod of ethylene vinylacetate (EVA) copolymer, covered by a thin EVA copolymer membrane. The implant measures 40 mm long by 20 mm outside diameter, contains 68 mg of ENG microcrystals and is marketed for three years of use. Mean maximum serum levels (813 pg/ml) are attained on day 4 after insertion [28]. Thereafter, ENG concentrations decline to ~ 196 pg/ml at the end of the first year and to 156 pg/ml at the end of the third year. Lower body weight is associated with higher serum concentrations. After removal of Implanon, serum levels of ENG fall below the detection limit of the assay (20 pg/ml) within a week. The dose of ENG is sufficient to inhibit ovulation in almost everyone for the full three years [28]. Implanon is highly effective [29]. Marketed in Europe and in some developing countries for a few years, there has as yet been no method failure reported. Bleeding patterns are similar to those associated with Norplant, i.e., irregular bleeding is common.

*3.3.1.3 Nestorone implants*

Subdermal implants containing nestorone are being developed by the Population Council and by South-to-South cooperation in Reproductive Health (Salvador, Bahia, Brazil), the latter using the trade name Elcometrine [28]. The Population Council implant contains a central core rod of nestorone and a silicone elastomer. An efficacy study of an early prototype [30] using two implants each containing ~ 80 mg nestorone reported no pregnancies during 1570 women months of use. A redesigned implant with an *in vitro* release of 110 – 115 µg/day is currently in clinical trials designed to determine whether full contraceptice effectiveness continues for 3 – 6 months beyond the 2 year life intended for the product [31]. By the end of February 2001, 151 women years of use had resulted in no pregnancies and there had been no first year failures. The current trials will be completed in early 2003.

An NES implant delivering ~ 100 µg NES/day has been tested for efficacy in breastfeeding women [32]. One hundred women in Chile used the implant (designed to last for two years) which was inserted between days 55 and 60 postpartum. 100 breastfeeding women using a standard copper IUD acted as the controls. During more than 2100 women months of exposure with each method there were no pregnancies. Discontinuation rates were similar but 25% of the NES discontinuations were for irregular bleeding. There was no effect of either method on infant feeding patterns but the mean duration of lactational amenorrhoea was higher among the implant users. NES serum concentrations reached a mean of ~ 175 pmol/l during the first month after insertion and decreased to ~ 60 pmol/l at the end of the first year. Concentrations in breast milk over the same time fell from 135 to 54 nmol/l.

Elcometrine contains 50 mg of crystalline steroid in a single silicone rubber capsule 4 cm long with a wall thickness of 0.8 mm and a diameter of 2.4 mm. Both ends are sealed with medical grade silicone adhesive [28]. Its effective life is only 6 months. It was registered as a contraceptive in Brazil in 1998 and is under study as a contraceptive implant for breastfeeding women.

*3.3.1.4 Uniplant*

Uniplant (South-to-South cooperation in Reproductive Health) is a single-unit implant delivering nomegestrol acetate from a single silicone rubber tube 39 mm long and 2.4 mm in diameter, sealed at both ends with medical grade silicone adhesive [28]. The current version contains 55 mg of finely ground steroid. The estimated release rate of the original version that contained 38 mg of steroid is ~ 100 ug/day during the first 3 months of use, with a decline to 70 µg/day during the last 9 months of use. It is recommended that each capsule be used for not longer than 1 year. A trial among 1803 women from nine countries contributing 19,900 months of use gave a one-year cumulative pregnancy rate of 0.94% [33] (Pearl Index 0.9/hundred women years). The discontinuation rate was 15.7%

### 3.3.2 Contraceptive vaginal rings

Steroid-releasing contraceptive vaginal rings were first described in the 1970s. They have the characteristics of other methods which avoid the oral route, but are under the control of the user who can remove, insert and discontinue the method at will.

*3.3.2.1 Ethinyl oestradiol and etonorgestrel*

NV Organon has developed a combined contraceptive vaginal ring releasing etonogestrel 120 µg/day and EE 15 µg/day over a period of three weeks of use (NuvaRing®). The ring is made of soft EVA copolymer, has an outer diameter of 54 mm and a cross-sectional diameter of 4 mm. Maximum concentrations of etonogestrel are reached after ~ 1 week after insertion followed by a gradual linear decrease to 21 days. If the ring remains in the vagina for 35 days, the linear decrease continues. Ethinyloestradiol concentrations show a similar pattern but reach their maximum ~ day 2 or 3 [34]. Suppression of ovarian activity is said to be similar to that achieved with an oral combined pill containing 30 µg EE and 150 µg desogestrel. In a one-year multi-centre study of contraceptive efficacy involving 1145 women using the ring for 12,109 cycles, there were six pregnancies, giving a Pearl Index of 0.6 (95% CI 0.24 – 1.41). Three of the six pregnancies were thought to have resulted from user failures [35]. Irregular bleeding, mainly spotting, varied between cycles but was never > 6.4%. Absent withdrawal bleeding occurred in a maximum of only 2.1% of cycles. Mean body weight increased by 0.43 ± 3.35 kg over the 13 cycles of treatment and the most frequently reported adverse events were vaginitis (13.7%), headache (11.8%) and leukorrhoea (5.9%). This method was

discontinued by 15% of women due to an adverse event. In a comparison with an oral COC containing 30 µg EE and LNG 150 µg (Microgynon 30; Schering) the incidence of irregular bleeding in the Nuvaring was significantly less (1.9 versus 38.8%; $p < 0.001$) [36].

### 3.4 Ethinyl oestradiol and norethindrone acetate

The Population Council has tested a silicone elastomer vaginal ring releasing 20 or 15 µg EE and ~ 1 mg norethindrone acetate. In a Phase II trial involving 61 women from three sites using the ring as a 21 + 7 day regimen for four months there were no pregnancies [37]. Serum progesterone concentrations indicated luteal activity consistent with ovulation in only one cycle but levels consistent with deficient luteal function occurred in 6% of cycles with the 15 µg EE ring which was associated with poorer cycle control.

#### *3.4.1 Ethinyloestradiol and nestorone*

The Population Council has tested a similar contraceptive vaginal ring using nestorone (100 µg) in combination with EE (30 µg) [38]. Phase II studies with a variety of dose regimens are ongoing.

#### *3.4.2 Nestorone-only vaginal ring*

Progestin-only pills have a half-life of ~ 19 h and demand a high degree of compliance for their effectiveness. The use of a vaginal delivery system allows the development of a low-dose progestogen-only method which does not rely on remembering to take a pill each day and which is under the control of the user. The Population Council has undertaken Phase II studies of a vaginal ring made of elastomer LSR 25 – 10:1 (Applied Silicone Corp, Ventura, CA, USA) containing a 3 mm diameter solid core of NES mixed with elastomer R2602 (NuSil Silicone Technology, Carpintera, CA, USA). Rings were designed to release 50, 75 or 10 µg/day [39]. Eighty-seven women volunteered for a 6-month study. Peak NES concentrations varied from 300 to 150 pmol/l according to the amount of NES and fell to between 220 and 100 pmol/l at the end of six months. All three doses inhibited ovulation. Luteal activity, detected in up to 2.6% of cycles, was usually suggestive of insufficient luteal function and was independent of dose. Serum oestrogen levels remained within the physiological range but tended to be lower with the highest dose. Like the nestorone-only implants the Population Council sees a role for NES rings for lactating women.

#### *3.4.3 Combined injectable contraception*

A once-monthly injectable contraceptive consisting of 25 mg medroxyprogesterone acetate (MPA) and 5 mg oestradiol cypionate has been developed by WHO [40]. Injections are administered intramuscularly every 28 days. The method has been licensed in some parts of the world for some years but is not yet licensed in Europe and is due to be launched in the US in 2002 as Lunelle™ (Pharmacia, Peapack, NJ, USA). In a direct non-randomised comparison of Lunelle with a widely used OC in the USA (Ortho-novum® 7/7/7 containing 35 µg EE in combination with 7 days each of 0.5, 0.75 and 1 mg norethindrone acetate), there were no pregnancies among 728 women in over 8000 cycles of use (compared with 1 pregnancy in 3400 cycles of pill use – Pearl Index 0.4) [41] this difference is not statistically different. Bleeding patterns were comparable with the COC. Bleeding episodes can be anticipated 18 – 22 days after injection and are induced by a decline in oestrogen concentrations to ≤ 50 pg/ml. Approximately 70% of women experience one bleeding episode per month, with only 4% experiencing amenorrhoea over three treatment cycles.

#### *3.4.4 Transdermal contraceptive patch*

Although HRT administration by transdermal patch has been available for more than a decade, the development of a contraceptive patch has lagged behind. A combined contraceptive patch has been very recently launched in the US (Ortho Evra™, Ortho McNeil) delivering 150 µg norelgestromin and 20 µg ethinyloestradiol daily [42]. A matrix patch consisting of three layers (an outer protective layer of polyester, a medicated adhesive middle layer and a polyester release liner removed before application) measuring 20 $cm^2$, each patch lasts 7 days. One patch per week for three consecutive weeks is followed by a patch-free week. In a Phase III trial comparing the patch to a triphasic oral contraceptive pill containing LNG, 571 women completed 13 cycles of patch use. The overall and method failure Pearl Indices were 1.24 and 0.99 respectively, not significantly different from those of the pill. For the patch, the cumulative probability of pregnancy after cycle 13 was 1.3 (0 – 2.7). After cycle 2 there was no difference in the rate of irregular bleeding when the patch was compared with the pill. In the first two cycles of patch use irregular bleeding and breast tenderness were both significantly more common than among pill users. The patch was also associated with a higher increase in total cholesterol and triglyceride concentrations at the end of treatment. In both groups, body weight had increased by 0.41 kg. Of women, 29.7% discontinued the patch or were lost to follow-up, 26% of these withdrew because of application site reactions.

#### *3.4.5 Intrauterine delivery systems*

In contrast to copper IUDs, the LNG-releasing intrauterine system (LNG-IUS) marketed in the UK and US as Mirena® (Leiras, Turku, Finland) is associated with a significant reduction in menstrual blood loss. Many women experience, and enjoy, amenorrhoea. Mirena now accounts for > 11% of the hormonal contraceptive market in the UK. Mirena is a relatively large device which can be difficult to insert into a small, nulliparous uterus. Attracted by the concept of using the IUS as a means of delivering the progestogen for HRT, Leiras has been working on developing a smaller frame. With a similar market in mind, others have been working on a frameless device.

#### 3.4.6 Frameless LNG-IUS

Fibroplant-levonorgestrel (Contrel Research, Belgium) consists of a 3 cm long by 1.2 mm wide fibrous delivery system releasing 10 µg LNG/day or a system of 4 cm in length delivering 14 µg LNG/day. The system is fixed to an anchoring thread by a metal clip 1 cm from the anchoring knot which is implanted into the myometrium. The tail of the thread protrudes through the cervical canal. The rate of release is constant over 5 years [43]. The 'system' has been tested in a small number of perimenopausal and postmenopausal women [43] and in women of reproductive age complaining of dysmenorrhoea [44]. The system was associated with amenorrhoea in all of the post menopausal women and most of those in the perimenopause. Women of reproductive age mostly reported reduced menstrual blood loss and dysmenorrhoea. Contraceptive efficacy has yet to be tested.

#### 3.4.7 3-Keto-desogestrel IUS

The Multiload Cu250 IUD (Organon) has been used as a device on which to mount three different doses of 3-keto-desogestrel with daily release rates of 1.5, 3 and 6 µg of progestogen [45]. The aim is to reduce menstrual blood loss, adequate contraception being provided by the copper IUD. Two hundred and three women participated in a double-blind study in which all three doses of 3-keto-desogestrel reduced menstrual blood loss by up to 40 ml after 12 months of use.

## 4. Antiprogesterones

### 4.1 Mifepristone

In 1980 a group of chemists at Roussel Uclaf, while looking for a glucocorticoid antagonist, discovered a synthetic steroid which was a potent antagonist of progesterone and cortisol but which had no antioestrogenic activity. They named it RU38486, abbreviated to RU486 or mifepristone. Mifepristone has a binding affinity five times that of progesterone and three times that of dexamethasone at the respective receptors. Over 400 compounds with antiprogesterone activity have been synthesised [46]. Only a handful have been tested on humans including mifepristone (formerly Roussel-Uclaf, now Exelgene), onapristone and lilopristone (Schering AG), the compound developed by the National Institute for Hormone Research (NIH), CDB 2914 and the Organon compound (see section 4.2).

Mifepristone (and the other antiprogestins) bind to progesterone receptors in the hypothalamus, anterior pituitary and uterus (both endometrium and myometrium). Once bound to the progesterone response elements of progesterone responsive genes, antiprogesterones render the gene transcriptionally inactive. The effects of antiprogestins depend on the dose and the time of the ovarian cycle when they are administered.

#### 4.1.1 Emergency contraception

The contraceptive effects of mifepristone have been demonstrated most clearly in trials of post coital (or emergency) contraception. A single dose of 600 mg given within 72 h of intercourse was shown to be 100% effective in preventing pregnancy [47]. The efficacy of emergency contraception can only be estimated since it is impossible to exclude conception of the pregnancy either before or after treatment. In a second study of 600 mg, the single pregnancy identified was deemed to have occurred with an act of intercourse which occurred after mifepristone treatment [48]. In a later dose-finding study, 10, 50 and 600 mg mifepristone all appeared to be equally effective in preventing pregnancy even up to 120 h after intercourse [49]. Side effects were independent of dose but menstrual delay (suggestive of delayed ovulation) was significantly less likely with the 10 mg dose. The mode of action of mifepristone used as an emergency contraceptive depends when it is taken. Given before ovulation it prevents it, given after ovulation the effect on the endometrium is highly suggestive of impaired implantation.

#### 4.1.2 Daily low-dose mifepristone

Mifepristone has been tested as a conventional contraceptive using a variety of regimens (daily, once-weekly and once-monthly). The theoretical advantages of once-weekly or once-monthly regimes include exposure to lower total doses of the drug but may be more difficult to remember. In each case, inhibition of ovulation and/or significant disruption of the normal endometrial histology is taken as an indication of contraceptive efficacy. It is fair to assume that anovulation will be contraceptive but the relationship between endometrial histology and the prevention of pregnancy is not clear. Exactly how 'abnormal' the endometrium has to look before implantation will fail is unknown and minor changes may not in fact be associated with contraceptive efficacy.

Doses of mifepristone from 10 – 0.1 mg have been tested as a once-daily regimen. Three doses, 10, [50], 5 and 2 mg [51-53] daily, have all been shown to inhibit ovulation. In a double-blind randomised trial comparing 2 and 5 mg in 90 women over 120 days in Scotland and China [53], Brown and colleagues (2002) demonstrated inhibition of ovulation in 90% of cycles with 2 mg and 95% with 5 mg. Sixty-five percent of women taking 2 mg/day and 88% taking 5 mg/day experienced amenorrhoea. Although follicular activity (and therefore oestrogen secretion) continued during treatment, the endometrium was rendered largely atropic suggesting that, even if ovulation did occur, implantation and conception would have been very unlikely. A dose of 1 mg/day of mifepristone inhibits ovulation only inconsistently but profoundly disturbs endometrial development [54], while 0.5 mg/day has no effect on follicle growth, ovulation, hormone secretion or the timing of menses but the endometrium appears retarded and glandular diameter significantly reduced [55]. The contraceptive efficacy of daily low-dose mifepristone has been demonstrated in only two studies. In the study from Scotland and China (using 5 mg mifepristone), 50 women used no method of contraception and there were no pregnancies [53]. In a study of 32 women using 0.5 mg mifepristone daily, 16 women

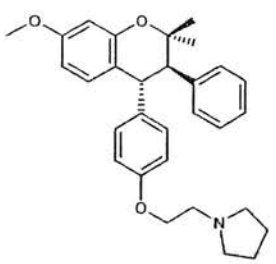

**Figure 1. Centchroman.**

completed six months of use. In 141 cycles, there were five pregnancies [56].

#### 4.1.3 Once-weekly mifepristone

An alternative approach has been once-weekly administration of mifepristone. Doses of 50, 25 and 10 mg [57,58] were associated with variable inhibition of ovulation while doses of 5 and 2.5 mg [59] did not inhibit ovulation. All doses, however, caused apparent desynchronisation of endometrial development and impaired secretory activity of the endometrium. The efficacy of a once-weekly regimen has been tested in only one study involving 18 women [60]. In over 63 cycles, three pregnancies occurred.

#### 4.1.4 Once-monthly mifepristone

The administration of mifepristone once-monthly is thought to prevent pregnancy by inhibiting implantation. A number of studies have demonstrated that 200 mg mifepristone given in the early luteal phase retards endometrial development without altering the timing of next menses. It also alters uterine contractility [61]. Two studies have tested the contraceptive efficacy of 200 mg mifepristone given within 2 days of the LH surge [61,62]. Efficacy in both studies was > 95%. The limiting factor to this approach is the accurate detection of the LH surge as the timing of mifepristone is critical. Given too early, it will delay ovulation resulting in prolonged cycles and a risk of pregnancy when ovulation does occur. Given too late, mifepristone induces endometrial bleeding and is probably much less effective in preventing pregnancy. The technology currently available to allow accurate detection of the LH surge demands a degree of compliance which appears to be beyond most women [63].

#### 4.1.5 Mifepristone plus progestogen

The administration of an antiprogesterone alone may theoretically be associated with the inhibition of ovulation while follicle development (and therefore unopposed oestrogen secretion) is maintained. This hormone environment is associated with an increased risk of endometrial hyperplasia and malignancy. These concerns have prompted trials of a variety progestins in combination with mifepristone, the progestin being given to protect the endometrium and to promote a regular bleeding pattern. A number of regimens have been tried including 25 mg mifepristone for 14 days followed by 5 mg norethisterone from days 15 – 24 [64]; 25 mg mifepristone for 21 days then 5 mg norethisterone or 5 mg MPA for days 22 – 31 [65]. However, most women ovulated in the progestin phase of treatment, presumably jeopardising contraceptive efficacy and irregular bleeding was common. 50 mg mifepristone on days 9 – 11 and 27 – 29 with 10 mg MPA on days 17 – 26 [66]; and a regimen comprising 5 mg mifepristone/day for days 1 – 15 with MPA 10 mg from days 16 – 28 [67]. A regimen comprising 10 mg mifepristone per day on days 1 – 15 with nomegestrol acetate 5 mg on days 15 – 28 did manage to confer regular cyclical bleeding but again ovulation was incompletely suppressed [68].

#### 4.1.6 Progestogen plus mifepristone

The opposite approach has also been tested, hypothesising that the administration of an antiprogesterone to women using progestogen-only methods may improve bleeding patterns and thereby enhance acceptability and continuation rates. In a double-blind placebo-controlled trial of 50 mg mifepristone taken once every 4 weeks by women experiencing troublesome irregular bleeding while using Sino-implant (Chinese Norplant) mifepristone shortened bleeding episodes but did not reduce their frequency [69]. Similar studies funded by WHO are ongoing.

### 4.2 Other antiprogesterones

Onapristone and lilopristone (Schering AG, Berlin), were both tested in humans for their potential effect on reproductive function but onapristone was abandoned after Phase I studies demonstrated changes in liver function and lilopristone has not been taken forward.

Organon has published data about two antiprogesterones, Org 31710 and Org 31806 [70]. Org 31710 is a potent antiprogesterone with low antiglucocorticoid activity and weak androgenic/anti-androgenic and anabolic properties. Single administration of 150 mg given every 28 days to 48 women using a desogestrel-only POP appeared to induce ovulation in 15% of subjects [71]. A trial of the effect on bleeding patterns of this regimen (akin to that of Cheng *et al.* with sino-plant [69]) has been completed but awaits publication.

CDB 2914 is an antiprogesterone developed by the National Institute of Child Health and Development (NICHD). It is a synthetic steroid analogue structurally similar to mifepristone. Doses of up to 200 mg have been shown to have no adverse effects in normally cycling women [72]. A single oral dose of 10, 50 and 100 mg of CDB-2914 given in the presence of a maturing ovarian follicle (14 – 16 mm in diameter) caused a dose-dependent delay in ovulation or follicle atresia and disruption of endometrial histology similar to that seen with mifepristone [73]. A trial of CDB-2914 as an emergency contraceptive is presently ongoing.

A new group of compounds called mesoprogestins (including J867, J956, J912 and J1042) have been synthesised and

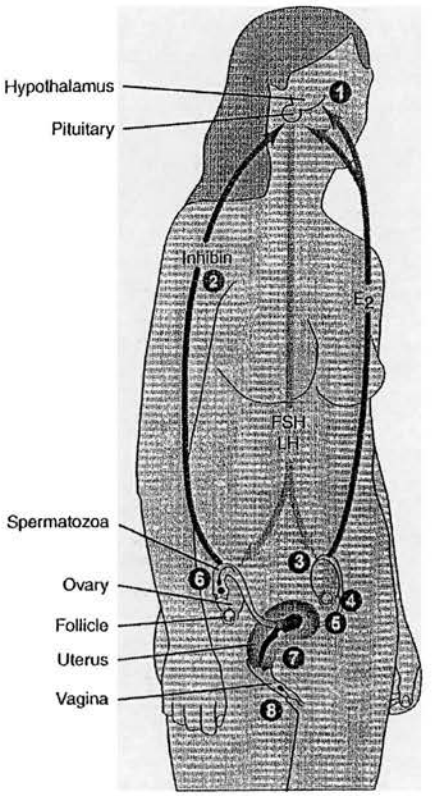


**Figure 2. Potential targets for contraception in women.** Reproduced with permission from Baird and Glasier [82].
FSH: Follicle-stimulating hormone; GnRH: Gonadotropin-releasing hormone ; LH: Luteinising hormone.

characterised (Jenapharm GmbH & Co, Jena, Germany). These compounds bind strongly to the PR but have mixed agonistic and antagonistic activities at PR *in vivo* [74]. Their antiproliferative effect on endometrium is being investigated in animal models including primates but no studies on humans have yet been published.

Although antiprogesterones hold much promise for a new approach to contraceptive development, progress is severely impaired by politics. Mifepristone is licensed in many parts of the world as an abortifacient and the anti-abortion lobby has been remarkably successful in scaring off both the pharmaceutical industry and the not-for-profit organisations, both of which continue to be reluctant to develop antiprogesterones for contraception.

## 5. Other antihormones

### 5.1 Gonadotropin antagonists

GnRH antagonists cause an immediate, rapid and reversible suppression of gonadotropin secretion inhibiting folliculogenesis and ovulation. These effects are clearly contraceptive but induce hypo-oestrogenism and, used long-term, oestrogen replacement would be required. There is great interest in the development of GnRH antagonists, including orally-active non-peptide compounds, with acceptable safety and 'commercial' profiles [75]. Already in use for short-term ovarian suppression in assisted reproduction, the market for these compounds will be benign gynaecological conditions such as endometriosis and fibroids and breast and prostate cancer. They will be expensive and the pharmaceutical industry appear reluctant to make them available for contraceptive development (for either men or women).

### 5.2 Anti-oestrogens

Anti-oestrogens are being developed for HRT and it is to be hoped that, in the not too distant future, a selective oestrogen receptor modulator can be developed for use in contraception. A compound which will inhibit ovarian activity without binding to receptors in breast or hepatic tissue would overcome the increased risks of breast cancer and VTE associated with the COC.

#### *5.2.1 Centchroman*

Centchroman (ormeloxifene; Figure 1) trans-1-[2-[4-(7-methoxy-2,2-dimethyr-3-phenyl]-phenoxy)-ethyl] pynolidine is a non-steroidal oestrogen antagonist with weak oestrogenic activity which prevents pregnancy in the rat, mouse, dog and rhesus monkey when administered within 24 h of coitus. It was developed at the Central Drug Research Institute in Lucknow, is marketed in India as a regimen comprising 30 mg twice-weekly for 12 weeks and once-weekly thereafter. It reaches peak concentrations in women within 4 – 6 h of administration and has a half-life of 7 days [76].

It has no effect on the hypothalamus-pituitary-ovarian axis, and doses as high as 120 mg/week fail to inhibit ovulation or disturb cyclical ovarian activity. It is thought to act by inhibiting implantation, specifically by accelerating ovum transport through the fallopian tube and preventing endometrial decidualisation, thus causing asyncrony between the arrival of the blastocyst in the uterine cavity and endometrial receptivity [77].

Centchroman has been reported to be effective in women as a postcoital contraceptive using a single dose of 60 mg. In a study of 103 parous women, using the method for 650 months only one pregnancy occurred [77]. Given once weekly 30 mg of centchroman used by 992 women for almost 14,000 months gave a cumulative pregnancy rate of 3.42 at 12 months. Prolongation of cycles was the commonest side effect associated within both post coital and monthly use. Since most pregnancies occurred during the first 12 weeks of the study the regimen was changed to allow twice-weekly dosing for the first 3 months successfully reducing the one year CPR to 1.63 [77]. The contraceptive effect is readily reversible.

From time to time various not-for-profit organisations have flirted with the idea of exploring centchroman in detail but none has yet done so.

## 6. Immunocontraceptive vaccines

The idea of a contraceptive vaccine has been around for a long time. Targets include sperm, oocyte and embryo. To date, immunisation against a variety of sperm proteins and against the zona pellucida of the oocyte have only been tested in animal models including primates [78]. Although there are more than 30 vaccines under development, many of them targetting male reproductive function, only a handful have been tested in women and all are anti-hCG vaccines. A vaccine using the unique CT peptide portion of BhCG as the antigen has been tested in India. Phase II studies have been published and demonstrate both contraceptive efficacy and reversibility [79,80]. WHO and one pharmaceutical company (Aphton, Miami, Florida) are undertaking Phase I trials of an anti-hCG vaccine. Progress with contraceptive vaccines has been hampered by a variety of factors including uncertainty about the long-term effects of immunising against human tissues and fears, perhaps ironically from women's groups, that contraceptive vaccines too easily lend themselves to coercive family planning policies. There also concerns about whether vaccines would ever achieve the effectiveness associated with long acting hormonal methods (such as implants) or modern IUDs.

## 7. Expert opinion & the future

As our understanding of reproductive biology increases there is now much interest in looking at genes whose products are solely concerned with reproductive processes and which therefore present prime targets for inhibiting conception (Figure 2). Methods which much more specifically target reproduction should produce contraceptives with fewer side effects. For review of potential targets see [81,82].

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ELSEVIER

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# Implantable contraceptives for women: effectiveness, discontinuation rates, return of fertility, and outcome of pregnancies

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**Abstract**

Progestogen-only contraceptive implants are highly effective. In most studies, 5-year cumulative pregnancy rates are less than 1.5/100 women for Norplant and Norplant II. No study has yet reported any failures with Implanon. Weight over 70 kg and age at insertion under 25 years both increase the failure rate of Norplant and Norplant II; however, data are as yet lacking for Implanon. The effectiveness of other progestogen-only implants for which there are as yet few data are unlikely to be any different. Continuation rates are high compared with other hormonal methods and with the intrauterine device. In most cohorts at least 35% of women, and often many more, are still using Norplant by the end of 5 years. Rates vary according to a number of factors, including population studied, age, and parity. Menstrual disturbance is by far the most common reason for discontinuation, with headache, acne, weight gain, and desire for pregnancy accounting for other common reasons for implant removal. Fertility returns rapidly following implant removal, and pregnancy rates (76–100% 1 year after removal) are usually no different from those following discontinuation of any other contraceptive method. There is no increase in the risk of ectopic pregnancy, fetal malformation, or impaired infant health in pregnancies conceived either during implant use or after removal.


*Keywords:* Contraception; Implants; Effectiveness; Continuation rates; Fertility

## 1. Introduction

Norplant was the first implantable contraceptive for women to be developed and is currently the most widely used. First tested in 1966, clinical studies have involved more than 55,000 women, and Norplant is registered in at least 60 countries. Norplant consists of six small, flexible, sealed capsules each containing 36 mg levonorgestrel (LNG). The initial studies were done with so-called "hard tubing" Silastic implants, but the currently used "soft tubing" results in a greater daily release and is associated with lower pregnancy rates [1]. Norplant is approved for use for 5 years. Norplant II (Jadelle) consists of two rods containing a total of 150 mg LNG and is licensed for use for 5 years of use. It is now registered in several countries in Europe. Two LNG implants, one composed of six capsules and the other two rods, are available in the People's Republic of China [2].

Implanon is a single implant that contains etonogestrel and provides contraception for 3 years. Implanon is registered in Australia, Indonesia, and in many countries in Europe.

Uniplant is a single implant delivering the progestogen nomegestrel acetate. It has been developed as a contraceptive, but is not yet registered in any country.

The Population Council is undertaking studies of the progestogen Nestorone as a contraceptive implant. A single nestorone implant (Elcometrine) is registered in Brazil for the treatment of endometriosis. For a detailed description of all the implants discussed in this article, see Croxatto, 2002 [3].

There has been a large number of studies of the efficacy of Norplant in a wide variety of different countries and in different population groups. There is a reasonable body of data on Norplant II; however, fewer data are available for Implanon and still less for Uniplant, Nestorone, and the Chinese implants.

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## 2. Efficacy

The effectiveness of a method of contraception is determined by how it works and how well and consistently it is used. A method that inhibits ovulation in every cycle in every woman who uses it will be 100% effective if it is used perfectly. Because most modern methods of contraception must be highly effective when used perfectly (or they would not be licensed), many of the pregnancies that occur during contraceptive use are the result of imperfect (or typical) use. Norplant, Norplant II, and Uniplant, and probably Nestorone, prevent normal sperm transport through the female genital tract; impair normal development of the endometrium; and in some, but not all, cycles inhibit ovulation [4]. Implanon has been developed by using a dose of progestin sufficient to inhibit ovulation in every cycle throughout almost the entire 3 years of use [4]. It also has an effect on sperm transport and endometrial development, but if there is no egg present to fertilize or to implant, these mechanisms of action are superfluous. Because all implants currently available are nonbiodegradable and have to be inserted and removed by a minor surgical procedure, compliance is guaranteed. Differences in failure rates between population groups are, therefore, unlikely unless there are significant differences in reproductive physiology or in the absorption or metabolism of the drug. This has not deterred the completion and publication of dozens of trials of efficacy in different countries and different settings throughout the world, all of which have reported similar results. A woman's age appears to influence the pregnancy rates of all reversible methods of contraception and may be a reflection of coital frequency (and of the inevitable decline in natural fertility with age) rather than of any inherent relationship between aging and the mode of action of the method. Because implant use makes no demands on compliance, the effect of age cannot be attributed to more reliable use, in contrast to, for example, oral contraceptives. The only other physiological variable known to consistently influence the efficacy of low dose progestin-only contraception is the weight of the user. Higher failure rates in some studies from some countries reflect a difference in the age and weight of the population participating in the trial.

### 2.1. Norplant and Norplant II

There is a vast literature on Norplant, although only the most recent studies have used the soft tubing formulation. In studies undertaken by the Population Council [1] in which recruitment was completed by 1986 (using hard tubing implants) and involving 2470 users, annual pregnancy rates/100 women were 0.2, 0.5,1.2, 1.5, and 0.8 through Years 1 to 5, respectively. In developmental studies undertaken from 1986 until registration of the drug, 1530 women using soft tubing implants were studied. There were no pregnancies during Years 2 and 5, and rates of only 0.1/100, 0.4/100, and 0.5/100 in Years 1, 3, and 4, respectively. The average pregnancy rate was thus significantly lower for the soft tubing implants. The risk of pregnancy was higher for women weighing more than 70 kg (1.7/100 in total) for the hard tubing implants. Prescribing information for currently available soft tubing Norplant implants describe the 5-year cumulative pregnancy rate as 3.9/100.

Much of the published data on soft tubing Norplant comes from studies comparing it with Norplant II. Different publications often overlap, and results from a group of women studied in one particular center and published in one particular article may also appear in another publication included in a different cohort of subjects.

In a multinational study undertaken in seven centers [5], 1198 women were randomized to Norplant (598 women) or Norplant II (600 women). There were no pregnancies during the first 4 years of use of either implant. During the fifth year, annual pregnancy rates were 1.0/100 women for Norplant II and 0.7/100 for Norplant, and because there were no pregnancies in the first 4 years, these are also the cumulative pregnancy rates. Both pregnancies occurring during Norplant use were in women weighing 70 kg or more at admission to the study, whereas the three pregnancies occurring among users of Norplant II were in women who weighed less than 70 kg. Thus, women weighing 70 kg or more when they first started using Norplant were more likely to experience a method failure ($p < 0.001$) than were lighter women. Among women aged under 30 years at the time of admission into the study, pregnancy rates were 0.15/100 women-years for the LNG rod and 0.16 for Norplant. For both methods there were fewer pregnancies among women aged 30 or over (0.11 and 0.00/100 years of exposure for LNG rod and Norplant, respectively).

In a study from North America [6] of 511 women, the cumulative pregnancy rate among Norplant users was 1.3/100 users. Three pregnancies occurred during Norplant use, two during Year 5 and one at Month 35 in a woman taking rifampicin—all three women weighed over 70 kg at the time of Norplant insertion. For women weighing 70 kg or more at the time of insertion, the cumulative 5-year pregnancy rate was 4.2/100, corresponding to an average life table rate below 1/100. Women under 25 years of age at time of insertion had a cumulative 5-year pregnancy rate of 2.8/100 compared with 0.7/100 for women aged 25 or over.

A large number of studies has been carried out in single centers or reported as findings from single centers. Five-year cumulative pregnancy rates range from 0 to 4.7/100 in these publications, which are summarized in Table 1 [6–16].

In a large study designed to undertake post-marketing surveillance [17], 7977 women using Norplant were followed prospectively alongside a cohort of women using locally available intrauterine devices (IUDs; 6625 women) and a cohort of women who had been sterilized (1419 women). Participants were recruited from 32 clinics in eight developing countries. Annual pregnancy rates each year for all three methods were less than 1/100 women-years. From

Table 1
Comparison of pregnancy rates*

| Country | Authors | Ref | Number of users | Cumulative 5-year pregnancy rate/100 users |
|---|---|---|---|---|
| Peoples' Republic of China | Gu et al. | 8 | 10,718 | 1.5 |
| Taiwan | Tseng et al. | 9 | 567 | 1.2 |
| Singapore | Singh et al. | 10 | 100 | 0.0 |
| Thailand | Chomopootaweep et al. | 11 | 308 | 4.2 |
| Indonesia | Affandi | 12 | 437 | 1.8 |
| Nepal | Chetri et al. | 13 | 407 | – |
| Bangladesh | Akhter et al. | 14 | 600 | 0.0 |
| Egypt | Shaaban | 15 | 3,000 | 1.8 |
| Belgium | Vekemans et al. | 16 | 612 | 3.7 |
| US | Sivin et al. | 6 | 511 | 1.5 |
| Pakistan | Rehan et al. | 7 | 265 | 2.5 |

* From reference [7].

Year 2 the annual cumulative pregnancy rate among Norplant users increased very slightly (0.08 in Year 2, 0.33 in Year 3, 0.35 in Year 4, and 0.59 in Year 5), and the overall cumulative pregnancy rate at 5 years was 1.46 ± 0.16.

Although Norplant was developed and is licensed as a method that lasts 5 years, there is good evidence for high efficacy persisting well beyond that time. In a study of Chinese women [8] involving 10,718 women in total, 3622 continued using hard tubing Norplant for a sixth year and 2433 for a seventh year. There were 18 pregnancies in the sixth year and 12 in the seventh, giving an annual gross pregnancy rate of 0.4/100 for both years. Beyond the fifth year, women aged less than 25 years at admission and those weighing more than 70 kg at the time of implant insertion were most at risk of pregnancy. Cumulative pregnancy rates at the end of 5 years were 1.53/100 and had increased only very slightly at the end of 7 years to 2.32/100.

In a second study of 1210 women using soft tubing Norplant for 7 years [18], the cumulative pregnancy rate was 1.1/100 at the end of 5 years, whereas at the end of 7 years it was 1.9/100. In the course of 7 years of use there was only one pregnancy among women aged 30–40 years at admission and that was in a woman who weighed 100 kg when she had the implants inserted (cumulative life table pregnancy rate of 0.4/100). No woman who weighed less than 50 kg at admission became pregnant during the study. Annual pregnancy rates were less than 1/100 continuing users in the sixth and seventh years of Norplant use.

### 2.2. Implanon

Data from studies undertaken during the development of Implanon [19] include a core data set of 13 studies that met the requirements for good clinical practice (GCP). These studies, involving 1716 women in at least 10 different countries, contributed 4103 women-years of use of Implanon in which no pregnancies occurred. An additional four studies not compliant with GCP bring the total exposure to 5629 women-years with no pregnancies. Ten of the studies used Norplant as a comparator, and over a total of 2155 women-years no pregnancies occurred during 3 years of Norplant use. Although obese women were purposely excluded from the studies, a small number of women (175) weighing over 70 kg participated in the developmental studies with no pregnancies during Implanon use.

Other publications also reported no pregnancies, but probably included data from some of the women who participated in the studies making up the core data set. Croxatto et al. [20] reported no pregnancies among 635 women using Implanon for 2 years and reported none among a group of 147 of these same women in whom use was extended to 3 years. Affandi et al. [21] also reported no pregnancies among 200 Indonesian women using Implanon for up to 4 years. Similarly, no pregnancies occurred among 100 Chinese women exposed to Implanon for 341 women-years [22].

### 2.3. Uniplant

Among 1803 women from nine countries contributing 19,900 women-months of use of Uniplant, there were 15 pregnancies, giving a 12-month cumulative pregnancy rate of 0.94% [23].

### 2.4. Nestorone

Among 1570 women-months of use of one of two prototype implants containing 76–82 mg nestorone each, there were no pregnancies [24]. Similarly, no pregnancies were reported among a cohort of breastfeeding women [25].

### 2.5. Efficacy of contraceptive implants compared with other methods of contraception

In a systematic review of implantable contraceptives, the National Health Service Research & Development Health Technology Assessment Programme (HTA) in the UK [26] searched relevant electronic databases for material on sub-

dermal contraceptive implants that was published between 1972 and July 1998. The publications were reviewed in the now standard manner for systematic reviews (for details, see French et al. 2000 [26]). All randomized, controlled trials (RCTs) and controlled clinical trials comparing implants with other forms of reversible contraception (including other implants) and all nonrandomized prospective cohorts were considered for inclusion in the meta-analysis. A total of 34 comparative studies met the inclusion criteria, including 15 RCTs and 19 nonrandomized prospective cohort studies. Most of these (59%) were carried out in community settings, although three studies recruited women while in the hospital (after childbirth or abortion). Two studies limited recruitment to adolescent women, and two others involved breastfeeding women. Data from 18 of the 34 studies were included in the meta-analysis, some of which have been referred to earlier in this review. Six studies compared Norplant with Norplant II, showing similar efficacy over 3 years of use. In the seven trials of Implanon versus Norplant, there were no pregnancies in either group and, therefore, no difference between the methods. Although the differences were not significant, there was a trend toward a lower failure rate among users of Norplant during both 1 and 2 years of follow-up when compared with women using either the combined pill or the copper-T IUD containing $\leq 250$ mm$^2$. A comparison of Norplant II with the LNG-IUS (intrauterine system) [27] showed no difference in pregnancy rates, and one study comparing Uniplant with the CuT 380A IUD [28] reported no pregnancies in just over 1200 women-months of use for each method.

In the study of soft tubing Norplant use for 7 years [18], pregnancy rates were compared with those among women who had been sterilized in the US Collaborative Review of Sterilization [29]. For women aged 18–34, the efficacy of Norplant was equal to that of sterilization. For women aged over 34 years, Norplant was more effective.

In the post-marketing surveillance study [17], Norplant was compared with copper and noncopper IUDs and with sterilization. The annual pregnancy rates fell year after year among IUD users, who had a cumulative pregnancy rate at 5 years of 4.19 ± 0.28 for copper IUD (13.0 ± 1.39 for noncopper IUDs) compared with 1.46 ± 0.16 for Norplant. Women who had been sterilized had a cumulative rate of 0.72 ± 0.23 at 5 years.

## 3. Continuation rates

Although there should be no difference in efficacy between different population groups of the same age and weight using the same method of contraception perfectly, differences in continuation rates are to be expected. For most methods of contraception, women taking part in prospective trials often have relatively high continuation rates because the inclusion criteria for trials tend to bias toward a willingness/likelihood to continue the method. Regular follow-up visits often serve as positive reinforcement (although for some participants the demands of too frequent follow-up are a cause of premature discontinuation). In many countries where health care is expensive, provision of free contraceptive supplies and services through clinical trials ensures good compliance. Data from "real life" are harder to come by, and loss to follow-up is common; even women taking part in the post-marketing surveillance study [17] were followed-up more assiduously than in average, normal practice. For most methods continuation rates vary between countries. Specific population groups (such as adolescents), too, may have a much greater tendency to discontinue a contraceptive method than other groups.

Table 2
Cumulative continuation rates with Norplant among per 100 US women by age in years*

| Age (years) | Year | | | | |
|---|---|---|---|---|---|
| | 1 | 2 | 3 | 4 | 5 |
| <25 | 91.6 | 70.1 | 52.6 | 40.8 | 29.0 |
| 25–29 | 86.4 | 74.2 | 60.0 | 45.3 | 37.8 |
| >30 | 87.0 | 77.7 | 72.2 | 61.4 | 51.7 |

* From reference [6].

### 3.1. Norplant and Norplant II

Sivin et al. [5] reported in 1998 cumulative life table continuation rates of 71% for both Norplant and Norplant II at the end of 3 years; 61% and 63%, respectively, at 4 years and 53% and 55%, respectively, at 5 years. Participating centers were in the US, Chile, Thailand, Finland, Singapore, and Egypt. Continuation rates were related to age, parity, and family formation factors. Menstrual disturbances were the most common reason given for discontinuation for both types of implant. Cumulative 5-year life table discontinuation rates for menstrual problems (including amenorrhea) were 16.4/100 for Norplant II and 19.2/100 for Norplant. Cumulative 5-year discontinuation rates for other medical reasons were 15.0 and 12.0/100 for Norplant II and Norplant, respectively. Headaches, weight gain, and acne together accounted for more than 50% of these other medical reasons for removal, with removals for acne and headache (but not for weight gain) varying significantly between clinics. All other medical reasons accounted for less than 1% of removals, with the exception of depression, which was cited by 1% of Norplant users as the primary reason for discontinuation.

In the study of Norplant in the US [6], the cumulative 5-year continuation rate was 39/100. Continuation rates varied with age and from Year two onwards were consistently lower among women under 25 years (Table 2). Five-year removal rates for specific complaints were 17.5/100 for menstrual irregularities, 3.9/100 for weight gain, 2.2 for headache, and 1.8 for mood change. Removal rates for all other medical reasons, including acne, were less than 1%.

Table 3
Cumulative continuation rates of Norplant in various countries*

| Country | Authors | Ref | Number of users | Continuation Rate/100 users | |
|---|---|---|---|---|---|
| | | | | Year 1 | Year 5 |
| Peoples' Republic of China | Gu et al. | 8 | 10,718 | 94 | 72 |
| Taiwan | Tseng et al. | 9 | 567 | 90 | 42 |
| Singapore | Singh et al. | 10 | 100 | – | 60 |
| Thailand | Chomopootaweep et al. | 11 | 308 | 98 | 71 |
| Indonesia | Affandi et al. | 12 | 437 | 96 | 78 |
| | Fisher et al. | 31 | 2979 | – | 34 |
| | Tuladhar et al. | 32 | 1283 | – | 33 |
| Nepal | Chetri et al. | 13 | 407 | – | 62 |
| Bangladesh | Akhter et al. | 14 | 600 | – | 41 |
| Egypt | Salah et al. | 33 | 250 | – | 58 |
| | Shaaban | 15 | 3000 | – | 51 |
| Scandinavia | Sivin | 34 | – | 76 | 33 |
| US | Sivin et al. | 6 | 511 | – | 39 |
| Pakistan | Rehan et al. | 7 | 265 | 86 | 46 |
| Belgium | Vekemans et al. | 16 | 612 | 87 | 36 |

* From reference [7].

In the cohort of women described by Sivin et al. in 1997 (centers in the USA, Chile, Thailand, Finland, Singapore, and Egypt [30]), continuation rates were 93.1/100 after 1 year, 83.3/100 at 2 years, and 71.3/100 at 3 years for Norplant compared with 93.8/100 at 1 year, 81.7/100 at 2 years, and 71.3/100 at 3 years for Norplant II. Once again, menstrual problems were the most common reason for removal, with acne, headache, weight gain, and depression being the most commonly cited other medical reasons.

Continuation rates have been shown to be particularly high in the People's Republic of China, where annual average rates of 90% have been reported with more than 70% of women still using Norplant at 5 years [8]. Half the women still using the method at 5 years opted to continue for a sixth year, and two thirds of those still using it after 6 years opted to continue for a seventh.

Although study design and recruitment criteria vary making published trials difficult to compare, there is a tendency for women in developing countries to have higher continuation rates with most methods of contraception when compared with women from developed countries (Table 3) [6,8–11,16,17,31–34]. As discussed earlier, the acceptability of a method varies considerably between cultures, and many other practical issues (access to other methods; cost of each method; and access to facilities for, and cost of, removal) besides the incidence of side effects, influence the likelihood of discontinuation. In a retrospective audit of continuation rates among new IUD and Norplant acceptors in Scotland [35], where all contraception is provided free with no consultation fee for insertion or removal of either method,, 2-year continuation rates among Norplant users were 72/100 compared with 55/100 among IUD users. None of these women were taking part in a trial. In a similarly designed retrospective audit undertaken in Belgium [16], 612 women had life table continuation rates of 87/100 at 1 year, 71/100 at 2 years, 53/100 at 3 years, 44/100 at 4 years, and 36/100 at 5 years. Twenty-three percent of removals were for menstrual irregularities.

### 3.2. Implanon

In a review of bleeding patterns drawn from data from the core data set, Affandi [36] reported an overall discontinuation rate for Implanon that varied dramatically in different parts of the world. Among 1716 Implanon users, discontinuation rates were 30.2% over 3 years in Europe and Canada, compared with only 0.9% in South East Asia. Similar findings were reported for Norplant use (22.5% versus 1.4%, respectively). Bleeding irregularities provided the most common reason for discontinuation of the method. Drawing from the same data set, Edwards and Moore [37] reported discontinuation rates for Implanon of 5.3% in the first 6 months, 6.4% in the second 6 months, 4.1% during months 13–18, and 2.4% during Months 19–24; thus, discontinuation tended to occur more frequently during the first year of use. In Indonesia, a total of 27% of women prematurely discontinued from the trial of Implanon, but only 3.5% discontinued during the first 2 years of use, and women continuing beyond that time chose to continue beyond the original study duration. In the cohort described by Croxatto et al. [20], 31% of women discontinued Implanon in the first 2 years of use, but only 6% in the extended third year.

### 3.3. Uniplant

Discontinuation rates for Uniplant were 15.7% at 1 year. Of the 276 women who stopped using the method prematurely, 37 (13%) did so to become pregnant [23].

### 3.4. Continuation rates compared with other methods

In the HTA meta-analysis [26], no difference in continuation rates over time could be identified between Norplant and Norplant II. However, at 1 year, Norplant users were nearly twice as likely to continue the method when compared with pill users (rate ratio 1.9; 95% CI 1.4–2.5) or with women using progesterone vaginal rings (rate ratio 1.8; 95% CI 1.3–2.4); and more than two-and-a-half times more likely to continue using the method than were women using Depo Provera. Continuation rates for Norplant did not differ when compared with the IUD. A comparison of Norplant II with the LNG-IUS [27] showed no difference in discontinuation rates. In the one study comparing Uniplant with the CuT 380A IUD [28] there were no differences in the discontinuation rates. In a recent paper analyzing the results of the 1995 USA National Survey of Family Growth [38], the percentage of women discontinuing Norplant by the end of 1 year was 12% compared with 22% for copper IUDs and 30% for injectable contraception. In a randomized, multicenter trial comparing Implanon with Norplant in Indonesia [39] involving 899 women, cumulative continuation rates were over 90% for both methods; 1.1% of Implanon users and 0.9% of Norplant users discontinued the method because of bleeding problems (including amenorrhea).

In the post-marketing surveillance study [17], women choosing Norplant continued with the method for an average of 4.2 years compared with 4.1 for IUD users (and 5.0—unsurprisingly—for women who were sterilized). By 5 years, 66.8% of women were continuing to use Norplant compared with 69.5% of those using a copper IUD. Menstrual problems accounted for the most common reason (13.7% discontinuations over 5 years) for removal of Norplant.

### 3.5. Continuation rates among special groups

There are no data for continuation rates of Implanon or Uniplant except for those from standard trials including women of reproductive years. There are, however, data for Norplant for specific population groups in the US. In a study of 181 poor teenage mothers who had Norplant inserted at some time during the first year after childbirth, 36% of women had the implants removed within 20 months [40]. "Concerns about adverse events" was given as the most important determinant of Norplant removal. In a study of 56 adolescents [41] choosing Norplant compared with 56 choosing the oral contraceptive pill, and despite 73% of women reporting menstrual irregularities, 1-year continuation rates for Norplant were 91/100 compared with 34% for the pill. Continuation rates from this group are extremely high, although of course users of implants are to some extent a captive population because the implants can only be removed by a health professional. Finally, in a study of urban minority women also from the US [42] the cumulative continuation rate among 197 black and Hispanic women were 83% at 6 months, 68% at 1 year, 39% at 2 years, 24% at 3 years, and only 13% at 4 years. Reasons for discontinuation included menstrual irregularities (44%), weight concerns (32%), headache (34%), and hair loss (23%).

## 4. Return to fertility

Women using Norplant, Jadelle, Uniplant, and Nestorone have incomplete and inconsistent inhibition of ovulation. As circulating concentrations of the steroid in Norplant decrease with time, ovulatory cycles are more likely to occur [43], and this is probably true of the other implants in this group. Implanon inhibits ovulation during most, if not all, of the 3 years of use for which it is registered. After removal of Implanon, serum concentrations of etonogestrel decline to below the limit of detection of the assay (20 pg/mL) within 1 week [44]. Ovulation [45] and fertility [46] are reported to return within 3 months after implant removal. In a pilot study of Implanon undertaken in Thailand [46] 6 women out of 29 who stopped using the implant and used no other method of contraception conceived within 3 months. All implants deliver low doses of progestogen that clear rapidly from the circulation when the implant is removed, with the consequent resumption of regular menstrual cycles and normal ovulatory ovarian activity in women who had normal ovarian function at the time of insertion. Fertility declines with age, and as with any method of contraception, some women who have used contraceptive implants for a number of years will have become naturally less likely to conceive after implant removal than they were at the time of insertion. Some may even have entered the perimenopause or menopause. For these reasons, there may be a few women who complain of infertility after implant removal, but use of the implant per se should have no detrimental effect on subsequent fertility.

In a study comparing the return of fertility following Norplant use with Norplant II, 9 out of 10 women using Norplant and 6 out of 11 women using Norplant II had conceived during 1 year of follow-up [47]. In a similar study comparing Norplant with the IUD, 11/14 ex-Norplant users conceived after 1 year and 75/78 after 2 years compared with three quarters of ex-IUD users after 1 year and 38/38 after 2 years [48]. When ex-Norplant users were compared with ex-depot medroxyprogesterone acetate (DMPA) users [49] pregnancy rates were no different (39/51 at 1 year and 46/51 by 2 years after removal of Norplant compared with 33/47 after 1 year and 42/47 after 2 years after stopping DMPA). The above studies were entered into the HTA meta-analysis [26], which could demonstrate no significant differences in pregnancy rates between Norplant, after removal, and all other methods of contraception, including DMPA.

Affandi et al. [49] undertook a prospective study of 51 Indonesian women who had Norplant removed because they

wished to conceive. Pregnancy rates among a cohort of ex-IUD and ex-DMPA users were simultaneously collected. There was no difference in the cumulative pregnancy rates, 76.5% of ex-Norplant users had conceived by 12 months (compared with 74.7% of ex-IUD users and 70.2% of ex-DMPA users), and 90.2% had conceived by 2 years (86.7% for ex-IUD users and 89.4% for ex-DMPA users). In a similar study in which 372 women were followed up after stopping contraception for planned pregnancy [50], pregnancy rates at 2 years were 87/100 for Norplant and 92/100 for Norplant II (compared with 88% for both the LNG-IUS and TCu380 Ag).

In only two published trials have pregnancy rates after removal of Norplant been below those accepted as "normal." In the post-marketing surveillance study of Norplant [17], 436 women using Norplant and 559 women using the IUD had their method removed because they wished to conceive. Two hundred fourteen women who had used Norplant (55.6%) and 291 women who had used the IUD (63.9%) became pregnant in the first year. Both these rates are low, and the difference between Norplant and the IUD was significant. However, pregnancy rates varied by site, and in four sites there were no differences in pregnancy rates between the two methods. The female/male sex ratio of newborn infants was significantly elevated, and under-reporting of pregnancies terminated for selective abortion may have occurred in some countries explaining the apparently low pregnancy rates for both IUDs and implants. The other study [51] reporting apparently low pregnancy rates after implant removal reported 1-year cumulative pregnancy rates after removal of Norplant of only 37.5/100 women and for Implanon of 48.8/100 women. Under-reporting of terminated pregnancies may also be the explanation for these apparently low rates.

## 5. Outcome of pregnancy

### *5.1. Outcome of pregnancy during implant use*

#### *5.1.1. Norplant*

In seven studies undertaken by the Population Council using hard tubing implants [1], 8 out of 46 pregnancies that occurred were ectopic, a 17% probability that a pregnancy would be ectopic and significantly higher than the rate for non-contracepting women. Subsequent studies with hard tubing implants, however, reported an ectopic pregnancy rate of only 1.3/1000 women-years [1].

In the study published by Sivin et al. in 1998 [5] comparing Norplant and Norplant II, there were no ectopic pregnancies among women using Norplant. From the US data set [6], also published in 1998, two pregnancies conceived during Norplant use went to term with the delivery of normal babies, and one was an ectopic pregnancy, giving an ectopic rate of 0.6/1000 woman-years.

In the post-marketing surveillance study [17], a total of 1737 pregnancies were recorded. Most (1134, 65.3%) were among women who has stopped using contraception. Six hundred three occurred while women were using a method (89 among Norplant users), and most of these ended in induced abortion. Seven pregnancies among women using no method were ectopic, giving a rate of 2.7/1000 women-years. For women who conceived while using Norplant, copper IUDs, or sterilization, the ectopic pregnancy rates were 0.3, 0.68, and 0.13/1000 women-years, respectively. One thousand one hundred nineteen pregnancies ended in childbirth, and 10 of them were multiple births. The mean birth weight of babies (49 live births) conceived during Norplant use was not different from that of babies conceived while no method was being used, and there were no malformations.

#### *5.1.2. Norplant II*

An ectopic pregnancy rate of 0.4/1000 was recorded by Sivin et al. [5], giving an 80–90% reduction in the risk of ectopic pregnancy compared with that observed for women using no method of contraception.

#### *5.1.3. Implanon*

There have as yet been no published reports of pregnancies conceived during the use of Implanon.

#### *5.1.4. Uniplant*

In the one published study of Uniplant, 15 women conceived during method use. Eight of the pregnancies were terminated. Seven went on to delivery, and all the babies were reported to be healthy [23].

### *5.2. Outcome of pregnancy conceived after removal of implants*

The outcome of pregnancy conceived after implant removal is no different from normal limits. There is no increase in the prevalence of malformations, birth weight, or the health of the infant [1,50–52].

## 6. Conclusions

In conclusion, low-dose progestogen-only implants provide a highly effective, reversible method of contraception with failure rates equivalent to those of sterilization. In the somewhat artificial context of clinical trials, continuation rates are good and are often better than those for other hormonal contraceptives or IUDs. By far, the most common reason for removal is menstrual disturbance. The return of fertility after discontinuation is rapid, and there is no evidence for any increased risk of adverse outcome (including ectopic pregnancy) of pregnancies conceived either during use of Norplant or Norplant II or shortly after stopping. More data are needed for Implanon and other implants that have been available for only a relatively short time or are

still under development, but any adverse effect would seem highly unlikely.

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# The Introduction of a New Contraceptive; Two Years Experience with Norplant

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**Abstract**

*Objective*

**To determine the uptake, acceptability and continuation rates of a new contraceptive implant, Norplant.**

*Design*

**Review of case notes of all acceptors during the two years following the introduction of the implant.**

*Setting*

**A large family planning clinic in Edinburgh.**

*Subjects*

**All women choosing Norplant.**

*Results*

**508 women chose Norplant, many as an alternative to sterilisation or because they had experienced problems with other methods of contraception. 9% of women were lost to follow-up. Of the remainder continuation rates were 84% at one year and 80% after 18 months of use. 43% of women gave bleeding problems as the reason for removal. However the combination of weight gain, mood swings, depression and headache was frequently reported as unwanted side effects by women seeking removal. No major problems were experienced with either insertion or removal of Norplant.**

**Conclusions**

**Norplant is an effective method of contraception which many women find attractive. The incidence of erratic bleeding is high but many women tolerate this problem because the method is easy to use and lasts five years. Careful counselling is essential for high continuation rates.**

## Methods

A record was kept of all patients who were counselled at length about Norplant and proceeded to insertion.

Counselling was undertaken by both doctors and trained family planning nurses, and included a detailed description of the method, its advantages and disadvantages, with particular attention being given to bleeding problems. A description of the insertion and removal procedures followed. Each patient was then assessed for their suitability for the method and an appointment given for insertion at least two weeks in advance. Discussion of side effects was repeated at the insertion visit.

Insertion and removal was carried out in all cases by fully trained doctors, or doctors training under supervision, in Family Planning Clinic premises, and an appointment given for follow up in three months. Patients were asked to return at regular intervals for review, and to attend at any time if they experienced problems.

**Results**

508 women had Norplant inserted in the two years following its introduction in July 1993. Many more came to the clinic for information and approximately 25% of those decided against the method for a variety of reasons, or were considered unsuitable. The age distribution ranged between 15 and 42 years with a mean of 26.7 years. 71% of women had live children.

**Introduction**

Norplant is a long-acting hormonal method of contraception which was introduced into the United Kingdom in 1993. Six flexible capsules releasing a low dose of levonorgestrel (30–35 mcg/24 hours after 18 months) are placed subdermally in the inner aspect of the upper arm under local anaesthesia. Insertion and removal are minor surgical procedures which require specialised training.

Norplant is a highly effective method of contraception with a cumulative failure rate over five years of 1.6 per 100 woman years[1] compared with a typical failure rate of the combined oral contraceptive pill after one year of use of 5.9/hwy.[2] The implant lasts for five years and fertility returns rapidly after removal.

Menstrual disturbance is the most frequently reported side-effect, and occurs in nearly all users. At £179 Norplant is expensive even if used for five years (£2.75/28 days against £1.52 for the most widely used modern pill). The additional cost is justifiable as the lack of need for compliance guarantees low failure rates. However long-term use is essential for cost effectiveness, and careful counselling, particularly about menstrual irregularities, is vital to avoid premature discontinuation.[3]

The launch of Norplant in the UK was accompanied by immense media interest and clinics in some parts of the country were said to have been 'inundated' with enquiries. We report the experience of a large family planning clinic in Edinburgh and describe the characteristics of those women who have accepted Norplant in the two years since its introduction.

18% (94) of women had a history of termination of pregnancy, with 6% (30) women having more than one termination, including one woman who had five.

Most women were using hormonal methods of contraception immediately prior to Norplant insertion. Women commonly chose Norplant as an alternative to sterilisation or because they had experienced problems with all other available methods of contraception.

*Insertion problems.* The insertion procedure was carried out using strict aseptic technique and usually took less than ten minutes. Most women found it an acceptable procedure. Two patients developed infection at the insertion site, both were treated with systemic antibiotics. In one of these women two capsules were expelled spontaneously from the insertion site. Blisters at the insertion site were reported by three patients, probably due to local reaction to the dressing strips. Hyperpigmentation of the skin over the site after sun exposure was experienced by two women who nevertheless chose to continue using the method.

*Failure rate.* No pregnancies have resulted from method failure, although two women were later found to have been pregnant at the time of insertion.

*Side effects and continuation rates.* 280 women had Norplant inserted more than one year ago. 27 women (9%) have never returned to the clinic on any occasion since insertion. 71 women (25%) are very satisfied with the method and have no perceived problems including 30 who had regular cycles and 14 who had amenorrhoea at one year. The incidence of side effects is shown in Table I. The most commonly reported side effect was altered vaginal bleeding, which was experienced by at least 70% of patients, and varied from complete amenorrhoea to continuous bleeding. There were no reports of heavy bleeding, the most common complaint being of irregular loss (25%). No diary cards were issued and no attempt has been made to quantify bleeding patterns. Only 30% of those reporting bleeding problems described the bleeding as troublesome. 45 women (16%) have requested removal, giving continuation rates after one year of 84%. 51 women have now had Norplant for 18 months, and 10 of these have requested removal, a continuation rate at 18/12 of 80%.

**Table I: Side Effects of Norplant**

| *Complaint* | % |
|---|---|
| Bleeding | 30 |
| Amenorrhoea | 20 |
| Weight gain | 6 |
| Headache | 4.5 |
| Acne | 4 |
| Bloating | 3 |
| Mood swing | 3 |
| Hair loss | <1 |
| Hirsutism | <1 |
| Abdominal pain | <1 |

*Removals.* Since the service started a total of 66 removals have been carried out in the clinic. Nine of these had Norplant inserted elsewhere but were referred from general practitioners or hospital doctors who lacked the expertise to remove Norplant themselves. The average duration of use was 39 (range 4–92) weeks. Most women gave more than one reason for requesting removal, and although bleeding problems were the commonest complaint, the combination of weight gain, mood swings, depression and headache occurred frequently, and accounted for 56% of removals (Table II). Difficulty was experienced with only two removals, one which resulted from poor placement at insertion and one required a second attempt before removal was complete. Most removals were achieved in under 30 minutes.

## Discussion

Widespread publicity about Norplant led to many requests for information about the method. Women were attracted by the simplicity of use, the low failure rate, and the long-acting nature of Norplant. Just over half of them were looking for an alternative to sterilisation, but many had experienced problems with other contraceptive methods, in particular with compliance—many stated that they found it hard to remember to take a pill every day. Inevitably there were also those women who, having used a variety of methods in the past, had never found their ideal contraceptive.

**Table II: Reason for Removal of Norplant (n=66)**

| *Reason* | % |
|---|---|
| Bleeding | 43 |
| Weight gain | 35 |
| Mood swings | 21 |
| Headache | 16 |
| Acne | 10 |
| Planning pregnancy | 7.5 |
| Preferred sterilisation | 6 |
| Hair problems | 6 |
| Abdominal pain | 3 |
| Relationship ended | 3 |

In the first two years since Norplant has been available in the UK continuation rates have remained high. 84% at one year compares extremely favourably with continuation rates of other methods[4] (Table III). Norplant has to be removed surgically and women must attend the doctor if they wish to discontinue the method. It is much easier for example simply to stop taking the pill; indeed over 50% of women using the oral equivalent of Norplant, the progestogen-only pill, have discontinued by the end of one year. Continuation rates are also higher than those for the IUD and discontinuation of that method also entails a visit to the doctor. Moreover at least 70% of women in our series reported side effects but persisted with the method. It is possible that continuation rates are higher because pre-insertion counselling is more thorough. There is no doubt that the cost of Norplant, the time required to insert and remove the capsules, and unfortunately the fear of litigation have all played their part in encouraging a counselling routine that is often absent from discussions about other contraceptive methods. In contrast to all other methods of contraception a short trial of Norplant is financially prohibitive. Most women in our series persisted with Norplant often despite very disrupted and unpredictable bleeding patterns.

**Table III: Continuation Rates of All Contraceptive Methods at One Year—USA**

| | % |
|---|---|
| Combined oral contraceptive pill | 50–75 |
| Norplant | 82–92 |
| Depo-Provera | 60 |
| Progestagen only pill | <50 |
| IUD | 76 |
| Condoms | 73 |
| Diaphragm | 69 |

Tolerance began to expire after six months but many women were prepared to continue for at least one year before requesting removal. It is common for these women to express regret that such a good method has not worked for them. They would nevertheless still recommend it to their friends.[5]

Recently there has been widespread publicity about difficulties with Norplant removal,[6] particularly when attempted by untrained personnel, some possibly resulting in litigation. An easy removal depends entirely on correct placement of the capsules at insertion, and a comprehensive training programme in both insertion and removal techniques has been available free of charge from Hoechst-Roussel who market the drug. We have had no patients in whom removal has been impossible, and as described earlier, only two of which could be classed as difficult, both caused by inexperience of the technique at insertion.

Two doctors in our clinic are Norplant trainers and have been responsible for most of the insertions and nearly all removals, although the majority of medical staff are fully trained in insertion. As trainers, we have taught more than 300 other family planning doctors and general practitioners, and have inevitably accumulated more experience than others in removal. Those doctors who have inserted relatively few Norplant have not yet acquired removal experience, and may never do so, preferring instead to refer to a specialist centre, not only for removals but also for insertions in the future. If recurrent adverse publicity, particularly from the USA continues,[7] doctors will be deterred from offering the method to their patients, and women will be deprived of a safe, effective, and increasingly available method of contraception.

Advances on a six-capsule system are imminent. Implanon, one capsule containing a 3-keto-desogestrel and lasting two to four years, and Norplant II consisting of two capsules and lasting three to five years, are in the late stages of development and may be marketed in the next two years. Insertion and removal will be much quicker and easier. Careful counselling however will still be necessary as the side effects appear to be similar to original Norplant. Until the problem of menstrual disturbance is solved, it is difficult to see contraceptive implants gaining in popularity, particularly in younger, nulliparous women.

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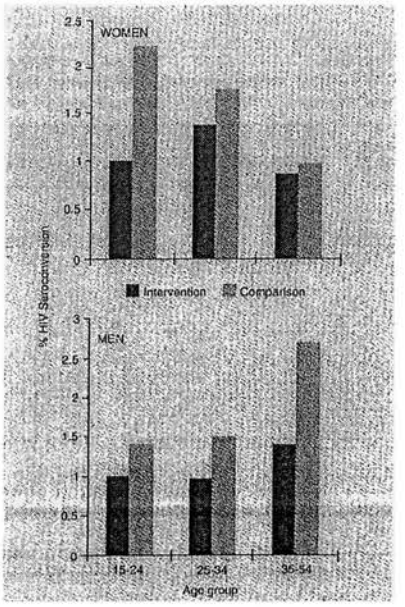


Figure 2: Incidence of HIV infection over 2 years by age and sex in intervention and comparison communities

## Training support, supervision, and monitoring

The syndromic strategy requires a new way of thinking from doctors and health workers. This can best be developed through short training seminars, followed by supervisory visits to health facilities during which the training is reinforced and errors in application of the flow charts are discussed.[6] Regular supervision is essential for success.

Another thing to be monitored is the effectiveness of the flow charts in use. The system therefore requires at least one reference clinic in place with access to microbiological laboratory services.

## Advantages of the syndromic strategy

Some critics have dismissed the syndromic strategy as 'unscientific', 'second class' or even 'quack medicine'. Although the strategy certainly has limitations, such statements are simply wrong. Unlike any other approach, it allows integration of STD services into the primary care structure and treatment of patients at the place and time of first contact with the health system. Waiting time is minimized; referral to a distant laboratory or specialist can be avoided. This in itself increases patient compliance dramatically. Many people in developing countries cannot spend money on transport or take hours off work.

The sensitivity of the approach is high, since by definition the diagnosis of a particular causal agent cannot be missed. What about cost-effectiveness? Because of the standardization, ineffective prescriptions (and thus drug wastage) are avoided. The increase in expenditure generated by the need to give combination treatments is by far outweighed by the savings on laboratory costs.[7]

The syndromic strategy has been adopted by many countries, particularly in Africa, where it has been well accepted and cure rates have been favourable. In Tanzania a randomized controlled trial showed that improved STD treatment using the syndromic strategy reduced the transmission of HIV infection in a rural population by 40% (figure 2). The rate of new HIV infections was substantially lower in all villages where the intervention had been applied, and that was true for all sex and age groups.[8] A reduction was also seen for syphilis and the urethritis syndrome.[9]

## Limitations

What are the drawbacks of the syndromic strategy? Most patients will be overtreated, since they are infected with only one of the microbes covered by the respective algorithm. Drugs need to be selected carefully with respect to side-effects.

One objection to syndromic management is the possible encouragement of bacterial drug resistance. However, bacterial resistance is usually caused by underdosage rather than over-treatment.

The main difficulty relates to the vaginal discharge syndrome, and to the frequently symptomless but dangerous infections of the cervix. Some vaginal infections are difficult to treat, and vaginal symptoms are not predictive for cervical infections. Here there is an urgent need for simple and cheap diagnostic tests.

STD control is one of the main pillars of HIV prevention, and the syndromic strategy can be instrumental in achieving it. One day, simple and low-cost diagnostic tests will be available. Until then, the syndromic strategy seems the best alternative.

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# The levonorgestrel-releasing intrauterine system

*Anna Glasier*

One of the drawbacks of existing intrauterine devices (IUDs) is the effect they have on menstruation: menstrual periods tend to become heavier and last longer, and this is a common reason for requesting removal. The levonorgestrel-releasing intrauterine system (LNG-IUS) does not have this disadvantage. Developed by the Population Council, it was approved for use in Finland and Sweden in the early 1990s and in the United Kingdom in mid-1995, where the trade name is Mirena. The manufacturers refer to the device as a "system" to distinguish it from copper-bearing IUDs that do not release hormone.

The system has the same polyethylene frame as the Nova T IUD, but wrapped around the stem is a column of

levonorgestrel within a rate-limiting membrane (Figure 1). The column contains 46 mg levonorgestrel released at a rate of about 20 µg/24 h (compared with 50-80 µg/24 h for Norplant and 30 µg in Microval, an oral gestagen-only Pill marketed in the UK). The release rate falls to about 15 µg/24 h after 5 years. The LNG-IUS is marketed for use for 5 years in Scandinavia and 3 years in the UK. Trials have shown no decline in efficacy after 7 years' use.

## Efficacy

The LNG-IUS is at least as effective as modern copper-containing IUDs. In a randomized trial, cumulative pregnancy rates after 7 years were 0.5 per 100 woman years for the LNG-IUS and 1.0 for the Copper T380Ag.[1] Expulsion rates, at around 7 per 100 woman-years, are about the same as those for modern copper devices.

## Mechanism of action

The LNG-IUS exerts a strong progestational effect on cervical mucus and on the endometrium. The mucus becomes thick and impermeable to sperm while endometrium becomes thin and inactive. Another effect that, as with copper IUDs, may contribute to the contraceptive action is a localized inflammatory-type response in the endometrium.

## Side-effects

The local action of the LNG on endometrium accounts for the strong effect on menstruation. In women with menorrhagia (menstrual blood loss > 80 mL) the LNG-IUS reduced loss by 86% at 3 months and 97% at 12 months.[2] Discontinuations for prolonged bleeding or dysmenorrhoea are less than those for copper IUDs; nevertheless, many women do report spotting, which particularly in the first 3 months can be irregular, prolonged and troublesome. By the end of one year up to 20% of women have become amenorrhoeic. Many see this as a benefit; but, if women are not warned that it may happen, amenorrhoea can paradoxically be a reason for requesting removal.[1]

The risk of pelvic infection in association with the LNG-IUS is even lower than that with the modern copper IUD, perhaps because of the "impermeable" cervical mucus.[3] As with the copper IUDs, if failure occurs there is a small risk of ectopic pregnancy (ectopic pregnancy rates with the progesterone-releasing intrauterine devices were much higher).

The LNG-IUS does not inhibit ovarian activity but, as with the progestagen-only Pill and Norplant, ovulation may be inhibited and persistent ovarian follicles (sometimes large enough to be called cysts) come and go. In general these cause no symptoms.

Although the IUS delivers only a small dose of LNG into the uterine cavity, the steroid is absorbed and up to 30% of women who stop using the method do so because of metabolic side-effects such as acne, nausea, breast tenderness and mood changes.[4]

## Gynaecological applications

The LNG-IUS is an effective contraceptive which has the potential for other gynaecological applications.[5] It can be useful in the management of menorrhagia; it is said to reduce the incidence and growth of fibroids; and, surprisingly it seems to lessen the incidence of dysmenorrhoea (among those who continue to menstruate). Another possible

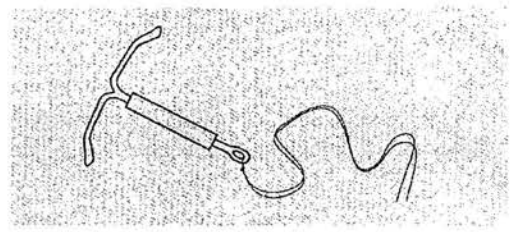

Figure 1: The LNG-IUS

application is in the management of endometrial hyperplasia and dysplasia, and it may alleviate premenstrual syndrome. The system is being tested as a route for administering progestagen directly to the endometrium in women receiving oral or transdermal oestrogen for hormone replacement therapy, in the hope that the low dose will have few systemic side-effects.[6]

## Conclusions

Despite its considerable merits,[7] the LNG-IUS does have drawbacks. It is expensive, just under £100 ($160) in the UK compared with under £10 for all copper IUDs. The barrel of steroid makes it big, the inserter is fat and insertion can be painful and difficult; some clinicians routinely use local anaesthesia for insertion but, even if this allows placement in a nulliparous uterus, immediate post-insertion discomfort may necessitate removal. The prolonged vaginal spotting can be troublesome. In our clinic we reserve Mirena mainly for parous women who have heavy periods and who regard more days of vaginal spotting as preferable to fewer days of heavy loss. The 20% who become amenorrhoeic think it is a wonderful contraceptive.

With time, technological advances will surely result in a smaller, perhaps even frameless, device. Though not quite the perfect contraceptive we were looking forward to, the LNG-IUS is an excellent method as well as having great potential for the management of certain gynaecological disorders.

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## Contraception

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# Contraception for the older woman

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Contraception often presents particular problems for women over the age of 40. An increasing incidence of menstrual problems may exacerbate the side-effects of some methods, such as the intra-uterine device (IUD), while advancing age compounds the risks of others, such as the combined oral contraceptive (COC) pill, which is relatively contra-indicated in women over 35 who smoke.

Fertility declines with age, and for women of 45 and over, it may be tempting to abandon contraception altogether as the likelihood of pregnancy recedes. However, when unplanned pregnancy does occur, it can be a disaster. Both childbirth and abortion are associated with a higher incidence of morbidity and mortality, there is an increasing risk of fetal malformation and the social and domestic consequences of unplanned pregnancy in later life can be devastating. Thus for many individuals, the benefits of stopping contraception must be weighed against the risks of getting pregnant.

## FERTILITY IN MIDDLE AGE

Faced with decisions about contraception, many women want to know their chance of conception. The record for the oldest recorded spontaneous pregnancy is said to be held by an American woman who gave birth at the age of 57 years and 129 days. Demographic statistics of fertility rates do not necessarily reflect natural fertility but depend on social trends in marriage and childbearing and contraceptive use. In the UK, although the average age when women marry and have their first child is rising, the number of women having children beyond the age of 40 is nevertheless falling. In Scotland in 1950, women aged 40–49 accounted for 4% of recorded births, while in 1990 they contributed only 1%. The decline in birth rates among older women over the 20th century reflects changes in social factors rather than in natural fertility. The ability to conceive has almost certainly not changed since 1950, merely the pattern of childbearing.

It is possible to get a better idea of natural fertility from populations with no artificial restraints on fertility, such as the Hutterites in North America who do not use contraception. Among these women, birth rates fall

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significantly after the age of 40, the average age of the last confinement being 40.9 years (Eaton and Mayer, 1953). However, even among populations who do not use contraception or abortion, fertility rates are affected by coital frequency, which tends to decrease with age and gynaecological conditions such as endometriosis or fibroids, which are more common among older women.

The effect of age on fertility is probably best reflected by surveys of normally ovulating women undergoing donor insemination. Most studies show that the rate of fertility decreases in the mid-30s and falls more markedly in women over the age of 40. Stovall et al (1991) reported that fecundity fell from 30% in women under 24 to 14% among women aged 40–45. Reasons for the decline in fertility include ageing oocytes and increasing pregnancy failure, probably resulting from an increased incidence of lethal chromosome abnormalities rather than from the inability of an ageing uterus to support a pregnancy.

## PATTERNS OF MENSTRUATION

The average age of the menopause in Western society is between 49 and 51 years. During the years leading up to the cessation of menstruation, ovarian cycles tend to change. From the age of 45, shorter cycles (under 24 days) become increasingly common, while the last years of the peri-menopause are often characterized by very long cycles (over 35 days). The probability of ovulation and therefore the risk of pregnancy in any one cycle is related more closely to cycle length than to a woman's age, long cycles being less likely to be ovulatory. In a study of women in New Zealand, Metcalf (1988) demonstrated that women over the age of 40 continued to ovulate in 98% of cycles, and steroid concentrations suggested that ovulation was normal. Once cycles become irregular, however, the probability of ovulation declines. In the same study, 31 women were followed from the first change in their regular menstrual pattern until the menopause; only 54% of cycles were ovulatory once a regular pattern was interrupted. The pattern of ovarian activity fluctuates, so that a woman who does not ovulate one month may do so in her next cycle. Indeed, four women in Metcalf's study ovulated in their last cycle before cessation of menstruation.

Anovulatory cycles are often accompanied by menorrhagia and menstrual problems, which are among the ten most common reasons for women of all ages consulting their general practitioner (Anderson and McPherson, 1983) and are particularly likely to prompt a consultation after the age of 40.

It is often difficult for a woman to know whether she has reached the menopause or not. Indeed, clinicians make the diagnosis in retrospect and not until 1 year after the last menstrual period. Spells of amenorrhoea may be followed by a recurrence of regular cycles, some of which may be ovulatory. After 3–4 months of amenorrhoea at the age of 47, there is an 87% probability that a woman will experience another bleed, but this falls to 70% by the age of 51 and 47% at 54 (Wallace et al, 1979).



## PREGNANCY OUTCOME AMONG OLDER WOMEN

When pregnancy does occur, it can be devastating if it is unplanned. In 1992 in Scotland, 271 pregnancies were terminated among women over the age of 40—just over 1.5% of all induced abortions.

A number of studies (e.g. Berkowitz et al, 1990) have confirmed an increase in pregnancy complications in primiparous women over the age of 35. Ante-partum and post-partum haemorrhage, pregnancy-induced hypertension and gestational diabetes are all significantly more common and are potentially life threatening. Peri-natal morbidity also increases, with a higher risk of premature delivery, low birthweight babies and multiple pregnancy. Even women having their first baby over the age of 30 have an increased risk of caesarean section and of the baby being admitted to the special care unit.

The incidence of chromosome disorders increases significantly among women in their late 30s and 40s. Down's syndrome is said to occur in 1 in 600 pregnancies among the general population, compared with 1 in 100 among women aged 40 and 1 in 40 after the age of 45.

Even if a woman chooses not to continue with her pregnancy, maternal morbidity and mortality associated with abortion also increase with the age of the mother.

## SEXUAL FUNCTION IN THE PERI-MENOPAUSE

The frequency of sexual intercourse declines with age after a maximum for women between the ages of 20 and 29. In their survey of sexual behaviour in Britain, Wellings et al (1994) described a median frequency of intercourse of five times every 4 weeks among women aged 35–44, falling to 2 per 4 weeks for married women and 4 per 4 weeks for co-habiting women from 45–49. More than 50% of women aged 50–59 reported no sex in the last month. The prevelance of sexual dysfunction in the general population is high and tends to increase with age (Bachmann, 1993), which may influence the acceptability of different contraceptive methods. Common complaints among women are poor vaginal lubrication during sexual arousal, with concomitant dyspareunia and a lessening of sexual interest and desire. In a community-based survey in the Oxford area, Osborn et al (1988) reported a history of sexual dysfunction (impaired sexual interest, infrequency of orgasm, dyspareunia or vaginal dryness) among 14% of women aged 35–39, 19% aged 40–44 and 32% among 45–49-year-olds.

Couples in a long-standing relationship may find that as the novelty is lost, their sexual activities become routine and lacking in spontaneity. Men, too, are more prone to develop sexual problems in middle age, and some couples become almost sexually abstinent. Barrier methods of contraception may exacerbate these problems, since the need to anticipate sex and the practicalities of using these methods sometimes interferes with arousal. Some women (at any age) respond adversely to the COC pill, complaining of mood swings or loss of sexual desire (reviewed in Bancroft, 1995). Such

problems seem to occur less often with the progestogen-only pill (POP), but erratic vaginal bleeding, particularly if it is frequent, may interfere with sexual activity. A number of studies have followed up couples after sterilization and demonstrated that many find their sex life enhanced by the removal of the fear of pregnancy (Bancroft, 1989).

## SOCIAL TRENDS THAT INFLUENCE CONTRACEPTIVE CHOICE

The structure of society is constantly changing. In Britain over the two decades from 1971 to 1991, the number of marriages declined by 16%, while the number of divorces more than doubled. In 1991 in the United Kingdom, one in every two marriages ended in divorce (Office of Population Censuses and Surveys, 1993). Couples are also divorcing sooner—almost 10% of divorces occur within the first 2 years of marriage. In consequence, the rate of remarriage is also increasing, particularly among men. Recently, too, it has become apparent that childbearing is not the ultimate aim of every woman, whether married or not, and one in five women is choosing to remain childless. These and other social trends inevitably influence contraceptive choice.

The pattern of use of the COC pill has altered since the early 1980s, with a steady increase in use by women under 30 and a fall among those over 30 years of age. Increased use of the condom reflects health promotion campaigns aimed at reducing sexually transmissible diseases, including HIV and AIDS, but may also reflect an increase in the average number of sexual partners and a reluctance to opt for a permanent method of contraception. In 1993, one quarter of women and one third of men reported using condoms in the preceeding year (Wellings et al, 1994).

## CONTRACEPTIVE USE

While the same range of contraceptive methods is available to all couples, typically different methods seem more appropriate to individuals at different stages of their reproductive lives. Thus patterns of contraceptive use change with age. In a survey of contraceptive use among British women who were sexually active, fertile and neither pregnant nor trying to conceive, Oddens et al (1994) reported that women over the age of 40 were less likely than younger women to be using a method of contraception at all. The increase in the prevalence of sterilization and the decline in pill use with age is outlined in Table 1, which summarizes the findings of the survey. Similar patterns were described by Wellings et al (1994) in their British survey. Generally speaking, in this survey, the popularity of condoms declined with age, while the popularity of male and female sterilization increased, reaching a peak among the 35–44 age group before falling slightly. Oral contraceptive use declined steeply with age, 44% of women between the ages of 25 and 34 reporting use in the previous year,



compared with 11% in the 34–44 age group. Married older women were less likely to use the pill than were women who were co-habiting.

Patterns of contraceptive use differ between countries, both as a reflection of availability and cost of methods, as well as of social factors. In a survey published in 1988 (Riphagen et al, 1988), 41% of women in Italy aged 40 and over used no method of contraception, compared with 16% in France and 7% in Great Britain. In the same survey, the condom was found to be the most popular contraceptive method among women over 40.

**Table 1.** Contraceptive use among British women aged 30–45 years.

| | Percentage using method | | |
|---|---|---|---|
| | Age 30–34 years | Age 35–39 years | Age 40–45 years |
| Oral contraceptive | 39.5 | 16.5 | 11.7 |
| Oral contraceptive and barrier | 0.5 | 0.6 | 0.0 |
| Barrier | 16.3 | 23.4 | 20.3 |
| NFP | 3.1 | 1.2 | 1.8 |
| IUD | 6.5 | 8.2 | 9.4 |
| Female sterilization | 9.5 | 19.1 | 18.9 |
| Vasectomy | 21.2 | 28.6 | 27.7 |
| None | 2.9 | 1.2 | 9.2 |

Adapted from Oddens et al (1994).

## CURRENTLY AVAILABLE METHODS OF CONTRACEPTION AND THEIR SUITABILITY FOR OLDER WOMEN

### Natural regulation of fertility

Natural family planning (NFP) is defined as the voluntary avoidance of intercourse during the fertile phase of the cycle in order to avoid pregnancy. It involves a continual awareness of fertility status using a variety of signs (basal body temperature, characteristics of cervical mucus and calender calculations, for example) to determine the fertile period. Motivation is essential for the successful use of NFP, and older women, perhaps in long-established relationships and with a reduced frequency of intercourse, might be expected to experience lower failure rates than younger couples using these methods. The World Health Organization prospective study of the ovulation method (World Health Organization, 1981) reported a significantly lower failure rate among couples whose family was complete, compared with those who wanted more children and were using the method in order to delay their next pregnancy.

Natural methods are, however, more difficult for older women to use, as irregular cycles and an increase in the prevelance of anovulation or cycles with an inadequate luteal phase make the signs of fertility much harder to detect. Recent research initiatives in the area of NFP are aimed at using scientific techniques to determine the fertile period with a greater degree of accuracy to allow a shorter period of abstinence. Home hormone-testing kits, for example, enable measurement of the luteinizing

hormone (LH) peak or of progesterone to diagnose ovulation. Even these may not help the woman with irregular cycles, as many of the kits are designed (and priced) for use for just a few days around the anticipated time of ovulation and would be impractical for use for prolonged periods of time.

### Barrier methods

Diaphragms have declined significantly in popularity since the 1960s and are nowadays only used by around 1–2% of sexually active women (Office of Population Censuses and Surveys, 1991). However, they are relatively more popular among older women, many of whom may be long-term satisfied users who rarely consult medical advisers. Although the quoted failure rates of the diaphragm are relatively high, the risk of failure is substantially lower in older women as natural fertility declines (Vessey et al, 1982). Use of a diaphragm requires initial fitting by a trained health professional. Thereafter it is entirely under the control of the individual woman, and sustained motivation is essential for correct use. The presence of abnormal pelvic anatomy, particularly prolapse of the vaginal walls, can make secure fitting and retention of the diaphragm more difficult. Cervical caps, which are more precisely fitted directly onto the cervix, or arcing diaphragms may overcome this problem.

Use of an adjunctive spermicidal preparation is always recommended to improve the efficacy of female barrier methods. This adds to the 'messiness' of the method, which many women dislike, but it may be beneficial in providing lubrication during intercourse if vaginal dryness is a problem for the older woman.

Use of spermicide alone for contraception is only recommended at times of extremely low fertility, such as for women awaiting the calendar year following their last menses or in conjunction with hormone replacement therapy (HRT). The 'Today' contraceptive sponge is a polyurethane foam impregnated with the spermicidal agent nonoxynol-9, which is placed high within the vagina. Although a method that women generally find highly acceptable, it has never been widely advocated in the UK because of a reportedly high failure rate. North American studies, however, have not found such a significant difference in failure rates between diaphragm and sponge users (Trussell et al, 1993).

Condoms are widely available and offer protection against pregnancy, sexually transmissible infection and cervical neoplasia. Older couples are generally more proficient in their correct usage, and failure rates of condoms fall considerably with increasing age of the user. Some older men find condoms help to enable them to maintain an erection, although others find they may exacerbate erectile impotence. Hypersensitivity to latex rubber can occasionally develop in either partner, and non-allergenic sheaths can be obtained. All sexually active women, irrespective of age, should, when embarking on a new relationship, consider the need for condoms as personal protection against sexually transmissible infection.





### Intra-uterine devices (IUDs)

Modern IUDs offer extremely reliable and relatively cheap contraception. They are less widely used in the UK at all ages compared with many other western European countries, and only 7% of sexually active women in the UK aged between 40 and 44 years use an IUD, compared with 26% of women in Sweden (Riphagen, 1988). An IUD can be inserted in an older woman requiring contraception, including in the peri-menopause, as age alone does not represent a contra-indication. Older women using an IUD have lower rates of pregnancy, expulsion, infection and perforation. Particular attention must be paid to an older woman's pre-existing menstrual pattern before fitting an IUD. If a woman already has dysfunctional uterine bleeding, menorrhagia or dysmenorrhoea, the increase in menstrual blood loss or pain associated with copper IUDs may be unacceptable.

Most copper-bearing IUDs have an effective lifespan in excess of the manufacturer's recomendations of 3 or 5 years (Newton and Tacchi, 1990). A copper-bearing IUD inserted after a woman's 40th birthday can remain in situ until a year following the menopause and thus provide continuing contraception without the need for replacement over these years (Tacchi, 1990). Less frequent insertions of IUDs reduce cost, inconvenience, pain and upset to the woman concerned, probably reduce the risk of infection, since it is at the time of insertion that this is greatest, and may result in a greater acceptability of IUDs, particularly in older women whose families are complete and who want a method that will last them up to the menopause.

Removal of an IUD is always ultimately recommended after the menopause to avoid confusion if post-menopausal bleeding occurs and because the device could theoretically provide a focus for sepsis, particularly with actinomycosis-like organisms. Removal becomes increasingly difficult as the uterus involutes with age but may be eased by the administration of one or two courses of HRT prior to attempted removal.

The levonorgestrel-releasing intra-uterine system (LNG-IUS) was only licensed for use as a method of contraception in the UK in 1995, although there has been over 12 years experience of its use in Scandinavia. The LNG-IUS, in contrast to other IUDs, confers positive health benefits that may be particularly relevant for the older woman. It offers highly effective contraception in conjunction with a dramatic reduction in amount and, after the first few months, in duration of menstrual blood loss (Andersson et al, 1994). One study has shown a reduction in menstrual blood loss of 86% after 3 months and 97% after 12 months (Andersson and Rybo, 1990). The reduction in menstrual blood loss associated with the LNG-IUS is considerably greater than that achieved by any other medical method. This method of contraception is therefore a particularly attractive option for older women with menorrhagia. A small British study has also shown where the LNG-IUS was fitted in women known to have fibroids, a reduction in menstrual blood loss occurred in conjunction with a reduction in size of the fibroids of approximately 25% on ultrasound measurement (Singer and Ikomi, 1994).

Use of an LNG-IUS can be continued into the peri-menopause and, indeed, used as part of an HRT regime. Several studies have looked at the LNG-IUS in combination with systemic oestrogen for this indication and found adequate endometrial protection, although unscheduled bleeding in the first few months of use was problematic (Raudaskoski et al, 1995; Suhonen et al, 1995).

### The combined oral contraceptive (COC) pill

The COC is the most popular method of reversible contraception in the UK because it is effective, easy to use and gives excellent cycle control. Many of the advantages of the COC are of particular relevance to older women. Regular, predictable periods that are often lighter than normal, relief of dysmenorrhoea and reduction in pre-menstrual symptoms are of particular benefit as menstrual dysfunction becomes more of a problem with age. Women are increasingly becoming better informed about the pill and many now value the protection it confers against endometrial and ovarian cancer (reviewed in World Health Organization, 1992).

From the mid-1970s, following the identification of an increased risk of cardiovascular disease, particularly myocardial infarction (MI) and stroke, women in the UK were usually advised to stop using the COC when they reached the age of 35 (30 if they were cigarette smokers). In the USA, the Food and Drug Administration (FDA) advised that women over 40 be urged to use some other form of contraception. In late 1989, however, these restrictions were removed by the FDA for women who were healthy and did not smoke. The pill had become safer for three reasons (Fortney, 1990). First, the dose of oestrogen had been reduced. Modern low-dose pills contain 20–35 μg oestrogen, and it has been clearly demonstrated that the risk of both MI (Croft and Hannaford, 1989) and thrombotic stroke (Lidegaard, 1993) is much less than that for pills containing 50 μg oestrogen. Second, the prescribing of the COC has become more sophisticated and women have become better informed about the risks, so that it is unusual for a woman with significant risk factors to be using the pill. Third, the incidence of both MI and stroke have declined quite substantially among young women since the 1970s (Fortney, 1990), Indeed, at least two large studies have shown that long durations of oral contraceptive use are not associated with an increased mortality (Vessey et al, 1989; Colditz, 1994).

The advent of low-dose combined pills containing the so-called third-generation progestogens was thought to enhance the safety of the pill and further reassure healthy women without risk factors for cardiovascular disease of their ability to continue using the pill up to the menopause. Third-generation progestogens are associated with fewer androgenic side-effects and appear to produce fewer adverse effects on carbohydrate and lipid metabolism. In particular, their use is associated with an increase in circulating concentrations of high density lipoproteins and a reduction in low density lipoproteins, a balance thought to be cardioprotective (Rebar and Zeserson, 1991). However in October 1995, following consideration of



three unpublished studies (one of which was unfinished), the Committee on Safety of Medicines in the UK issued a recommendation that combined oral contraceptives containing the third generation progestogens desogestrel and gestodene should no longer routinely be prescribed (Carnall, 1995). All three studies had independently concluded that the risk of venous thromboembolism was increased by as much as double among women using these pills compared with women using combined pills containing the older progestogens levonorgestrel and norethisterone. There has been much discussion as to whether this decision was justified particularly since all three studies were said to have the potential to detect any clinical benefit in terms of risk of arterial disease (myocardial infarction and stroke) a potential which may now not be fulfilled certainly in the UK. Only one very low-dose (20 μg of oestrogen) third generation pill is available (Mercilon). It appears to be as effective as the 30 μg pills but, as might be anticipated, is associated with a higher incidence of cycle irregularities such as breakthrough bleeding (Akerlund et al, 1993). Cycle control however usually improves after a few months and the modern 20 μg pill was probably the preparation of choice for women over the age of 35 who wished to continue using the combined pill. Unfortunately the second generation equivalent (Loestrin 20) is reported to have a higher failure rate and to confer poor cycle control (Guillebaud, 1995). It is not clear whether the effect of gestodene and desogestrel on the risk of VTE is an inherent property of these particular progestogens or a result of their interaction with oestrogen. If the latter is the case then 20 μg of oestrogen even in combination with a third generation progestogen may confer less risk than 30 μg in combination with an older progestogen.

Prolonged use of any combined pill will of course mask the onset of the menopause since oestrogen withdrawal bleeds will continue as long as pill use does.

While the COC indisputably protects against ovarian and endometrial cancer, there are still concerns that its use is associated with an increased risk of breast cancer. A World Health Organization scientific group (1992), convened to advise on steroid contraception and the risk of neoplasia, concluded that numerous studies had shown no overall association between oral contraceptive use and breast cancer, and in particular that there is no increased risk among women over the age of 45. A number of recent studies have, however, suggested a possible association between long-term oral contraceptive use and breast cancer diagnosed before the age of 36. This appears to be of particular concern when pill use starts at a young age (under 20 years) (La Vecchia, 1992). It has been suggested that the COC may accelerate the development of breast cancer in women who are already at risk. If these observations are substantiated, women over 35 who have been taking the pill for some years and wish to continue may be reassured that they are probably not altering their risk of breast cancer any further. If, however, COC use in some way promotes or accelerates the growth of pre-existing breast tumours, older women who start the combined pill for the first time may be at risk of an earlier diagnosis of cancer.

## Progestogen-only contraception

Hormonal methods of contraception that contain progestogen alone are particularly useful for women with relative contra-indications to oestrogen such as obesity or cigarette smoking, which become more significant when combined with advancing age. The POP (or mini-pill) has an added advantage in that the total dose of progestogen is less than that in the equivalent combined preparation. Microgynon, for example, is a COC pill that contains 30 μg oestrogen and 0.15 mg norethisterone. The daily dose of norethisterone in the equivalent progestogen-only preparation, Microval, is 0.03 mg. Even allowing for 21 days of combined pill use compared with 28 of POP use, the total dose of norethisterone over 28 days of Microval (0.84 mg) is less than one third that of the combined preparation (3.15 mg). At present, there are no oral progestogen-only preparations marketed containing one of the third-generation progestogens.

While the POP is associated with an overall failure rate of 2–3 per hundred woman years, Vessey et at (1985) demonstrated a rate of only 0.3 per hundred woman years (as good as that that of the combined pill) among women over 40 years of age.

Long-acting progestogen-only contraceptives (injectables and implants) are less likely to be prescribed to new users over the age of 35. Indeed, the current data sheet for Norplant in the UK describes it as being suitable for women aged 18–40. The reasons for the upper age limit are not clear, since the very nature of Norplant makes it a useful method for couples who want no more children but who are not yet ready to consider sterilization.

All progestogen-only preparations are associated with menstrual disturbance—a problem already faced by many older women. Up to 20% of women will stop using the POP because of irregular, unpredictable and often frequent bleeding. There is little evidence that bleeding patterns improve with time, and changing brands of pills does not seem to help. Similar patterns are a feature of the LNG implant (Norplant) use, and it is unlikely that the new implant containing desogestrel (Implanon) will be any better. Many women tolerate the menstrual chaos associated with Norplant because of the reliability, convenience and long-acting nature of the method. It is likely, too, that women are better counselled about the side-effects of Norplant, and moreover the cost of the method (£179 in the UK) precludes a short trial of acceptability. In contrast, irregular bleeding is uncommon among women using Depo-Provera (DMPA), around 80% of whom will have amenorrhoea or infrequent scanty periods after 1 year of use. This may be seen as a particular advantage by women troubled by menorrhagia or polymenorrhoea associated with the peri-menopause.

There are much fewer data on long-term safety of the POP than of the COC. However, there are no known long-term risks of malignancy or cardiovascular disease. For many years, concern that DMPA might increase the risk of breast cancer limited its availability in many countries. In the UK, although licensed in 1984, its use was limited until 1995 to women for whom other methods of contraception were inappropriate and





for short-term use to cover, for example, rubella immunization or the waiting period following vasectomy. In the USA, DMPA was not approved for marketing until 1992 following the publication of large epidemiological studies in New Zealand (Paul et al. 1989) and in Kenya, Mexico and Thailand (World Health Organization, 1991), which found no significant overall association between DMPA and breast cancer. However, a recently published analysis of the pooled data from these two studies (Skegg et al, 1995) has described an increased risk of breast cancer among recent users of DMPA. Although the relative risk was highest for women younger than 35 years of age, the relative risk for women of all ages who had initiated DMPA use within the last 5 years was nevertheless 2.0 (95% CI 1.5–2.8). The authors concluded that the observed increased risk of breast cancer might be due either to enhanced detection in women starting DMPA or to acceleration of the growth of pre-existing tumours. Since the risk of breast cancer increases with age, DMPA may not be a suitable choice of contraceptive method for a new user over the age of 40, particularly if she has any other risk factors.

Interestingly, while it might be supposed that progestogen-only methods of contraception, particularly high-dose methods such as DMPA, might protect against endometrial cancer, there are virtually no data to support this (McCann and Potter, 1994). There may be a modest degree of protection from ovarian cancer, although this is likely to be less than that conferred by the COC pill. A recent publication from France (Plu-Bureau et al, 1994) has suggested that progestogens might have a beneficial effect on the risk of breast cancer when used to treat women with benign breast disease.

It has been suggested that the chronic hypo-oestrogenism associated with long-term use of high-dose progestogen may lead to loss of bone mineral density (BMD) and an increased risk of osteoporosis. In a study from New Zealand (Cundy et al, 1991), women who had used DMPA for a median of 10 years were found to have a significant reduction in BMD in both the lumbar spine and the femoral neck when compared with pre-menopausal controls. BMD among DMPA users was significantly greater, however, than that of post-menopausal controls who had experienced a similar duration of hypo-oestrogenism. The study was small (only 30 women in each group) and there were significantly more smokers among the DMPA users. Moreover, at least one previous study had suggested that medroxy-progesterone acetate might be effective in preventing post-menopausal osteoporosis (McNeeley et al, 1991). Cundy et al, however, published a second (even smaller) study in 1994 demonstrating an increase in BMD among 14 women who stopped using DMPA, suggesting that the original observation was likely to be correct even despite the shortcomings of the study. Given these concerns, a large prospective study of the effects of Depo-Provera on BMD is being undertaken in the USA. In the UK, it has been suggested that women who are amenorrhoeic on long-term Depo-Provera should should take oestrogen replacement in the form of trans-dermal patches if a single measurement of serum oestradiol concentration is in the post-menopausal range. This seems to transform Depo-Provera

into a complicated and relatively expensive method of contraception unsuitable for women with contra-indications to oestrogen. Since the loss of BMD—if it occurs at all—appears to be reversible, a simpler approach may be to advise women using the method to stop at the age of 45 years in order to allow a recovery of bone density before the menopause. Whether women who experience amenorrhoea while using the POP or Norplant are at risk of osteoporosis is not known, but a small study of women during lactational amenorrhoea (Caird et al, 1994) demonstrated a protective effect of the POP on BMD.

It might be assumed that the use of hormonal contraception containing oestrogen would, in contrast, protect against osteoporosis. Although there are several studies that demonstrate a beneficial effect of the combined pill, even of preparations containing only 20 μg oestrogen (Mais et al, 1993), there are many that fail to demonstrate such an effect (reviewed in Mehta, 1993). While a triphasic oral contraceptive preparation has been shown to be effective in preventing bone loss when administered to post-menopausal women (Shargil, 1985), most studies have been unable to detect any difference in BMD after the menopause between women who have used the combined pill during their pre-menopausal years and those who have not (Fortney et al, 1994). While COC use may increase BMD pre-menopausally, the effect may not be sustained once natural bone loss occurs after the menopause.

### Sterilization

Sterilization is the most common method of contraception among women over 35 years of age in the UK (Office of Population Censuses and Surveys, 1993). In 1991, almost 50% of women aged 40–49 years were sterilized. Currently, male sterilization is slightly more popular (13% of couples) than female sterilization (around 12% of couples), particularly among couples under the age of 45.

Both methods are, of course, regarded as permanent. The choice of which partner opts for sterilization depends on a number of factors. Of relevance is the fact that a woman's natural reproductive life is effectively over by her mid- to late-40s, while a man remains potentially fertile well into his seventh or even eighth decade. With the current trend towards increasing rates of divorce and remarriage, this difference becomes more significant.

In the UK, female sterilization is usually performed laparoscopically under general anaesthesia, while vasectomy is usually carried out under local anaesthetic. In their statement on contraception for women over the age of 35, the International Planned Parenthood Federation (1995) states that 'As a general rule, vasectomy is a safer procedure than female sterilization.' While this is almost certainly true, partly because of the different anaesthetic techniques used, there remain more concerns about the long-term safety of male as opposed to female sterilization. A possible link between vasectomy and cardiovascular disease and other conditions related to the development of auto-antibodies (joint disease and multiple sclerosis, for example) was suggested in the 1970s. These fears have not been substantiated (Massey et al, 1984). An increase in testicular cancer among vasectomized men (Strader et al, 1988; Cale et al, 1990) has also not been borne out by a large study of over 73 000 Danish men (Møller et al, 1994). Perhaps of more concern is the increased risk of prostate cancer after vasectomy, which has been described in a number of large epidemiological studies (Editorial, 1991). Although both the World Health Organization and the National Institute of Health in the USA have reviewed the evidence for a link and have recommended no change in family planning policies, they have also recommended that more research is undertaken.



Female sterilization is not thought to alter ovarian function or menstruation. Although it has been suggested that menstrual disturbances are more common following sterilization, it is now felt that this is probably an effect both of advancing age and of the fact that many women who use the COC before sterilization complain of a deterioration in bleeding patterns as their natural cycles return. A number of studies have demonstrated an increased incidence of hysterectomy among women who have been sterilized (Templeton and Cole, 1982; Rulin et al, 1993). It seems likely that a woman who has already made the decision to have no more children would be more likely to accept, or even to seek, hysterectomy as a solution to her menstrual problems than would a woman who has not been sterilized.

## WHEN CAN CONTRACEPTION STOP?

In the light of the above discussion, it is clear that contraceptive precautions must be continued during the fourth decade of a woman's life if she is to be absolutely certain of avoiding unwanted pregnancy. Current recommendations are that non-hormonal methods of contraception should be continued until a woman has experienced 1 year of amenorrhoea if she is 50 or older and 2 years of amenorrhoea if she is younger (Whitehead and Godfree, 1992). Women who are using a hormonal contraceptive may have some difficulty deciding when they have reached the menopause. Use of the COC will ensure regular withdrawal bleeds regardless of menopausal status, while progestogen-only methods may induce amenorrhoea in women who have not yet reached the menopause. Biochemical tests of menopausal status may be difficult to interpret. The POP has little suppressive effect on gonadotrophins and will not usually relieve menopausal vasomotor symptoms, so that a history of the latter will help to make the diagnosis. Raised follicle-stimulating hormone (FSH) concentrations on two separate occasions in a woman taking the POP usually indicates ovarian failure. The oestrogen component of the combined pill will, however, mask menopausal symptoms and also suppresses gonadotrophin secretion. The COC must be stopped for about 6 weeks before FSH concentrations will give a reliable estimation of menopausal status, and it is probably wise to repeat the measurement on a second separate occasion (reviewed in Gow et al, 1994).

## HORMONE REPLACEMENT THERAPY (HRT) AND CONTRACEPTION

Many women are now starting (HRT) for menopausal symptoms and prophylaxis against osteoporosis before the menopause. These women need to continue contraception and, in this situation as with the combined pill, it becomes impossible to give accurate advice on when contraception can be safely discontinued as HRT will induce regular withdrawal bleeds and mask the rise in FSH concentrations. If a woman is prepared to stop HRT for 6 weeks, an FSH concentration can be checked after that time and the woman advised accordingly. If she is unwilling to discontinue HRT, contraception can be arbitrarily continued until she reaches the age of 55 years.

Contraception should be continued in women taking HRT who have not yet reached the menopause because the natural oestrogens contained in HRT preparations are of lower potency and dose than the synthetic oestrogen within the COC and do not reliably inhibit ovulation. One small study demonstrated biochemical evidence of ovulation in 60% of women given conventional oral HRT who previously had regular cycles (Gebbie et al, 1995). Early studies suggested that a daily oral dose of about 4 mg oestradiol was necessary to obtain acceptable contraceptive efficacy (Serup et al, 1981)—most standard HRT preparations contain 1 or 2 mg oestradiol. In contrast, one recent study that combined 1 mg micronized oestradiol with 150 mg desogestrel reported ovarian suppression over two cycles in 20 women, as monitored by ultrasound examination in combination with hormone assays (Wenzl et al, 1993). In women treated with subcutaneous oestradiol implants combined with cyclical oral norethisterone, significant follicular growth (measured by ultrasound) continued until the fourth treatment cycle (Magos et al, 1987).

There is considerable interest in the development of oral contraception using natural oestrogens, which, by nature of their weaker potency, have fewer adverse effects on fibrinolysis and coagulation mechanisms than do synthetic oestrogens, and which thereby carry less risk to older women and those with cardiovascular risk factors.

Methods of contraception available to women taking HRT who require additional contraception include barrier methods and IUDs. The POP can be given in conjunction with HRT, although there are no scientific data to support its use in this way. Although the dose of additional progestogen in HRT could theoretically be reduced if the POP were added, it is in practice easiest to recommend that both preparations are taken simultaneously without altering progestogen doses. As discussed earlier, healthy women with no risk factors may take COCs up to the age of 50 years to give effective contraception, excellent cycle control and relieve early menopausal symptoms.

## FUTURE DEVELOPMENTS

Many of the future developments in contraceptive technology (reviewed in Van Look, 1995) will be appropriate for older women. Some of the new





delivery systems for steroidal contraception, such as vaginal rings and skin patches, avoid the 'first pass' through the liver, allowing reduced doses of hormones and thus potentially reducing the risk of cardiovascular disease and venous thrombosis. The development of anti-hormones, such as anti-progestogens, removes the need for exposure to ovarian steroids, with their concomitant risks and side-effects. The use of these compounds as a once-a-month pill may be of particular value to older women with a lower frequency of intercourse. Contraceptive vaccines may provide an alternative long-acting method of contraception for couples who are undecided about sterilization, while the advent of a long-awaited hormonal method for men will undoubtedly meet the needs of couples who have difficulty finding any method that suits them.

While the need to provide safe methods of contraception has been of paramount importance for many years, it has only recently been suggested that such methods could—and should—be manipulated to provide positive benefits to reproductive health. The COC is extremely effective at reducing the risk of ovarian and endometrial cancer, and it may be that contraceptives of the future will be intentionally designed with similar positive side-effects, such that older women, rather than seeing the issue as an inevitable burden, will benefit from continuing to use contraception until the menopause.

## SUMMARY

Contraception presents particular problems for women over the age of 40. Although fertility is declining and the risk of pregnancy may be small, the consequences of an unplanned pregnancy may be socially devastating and medically ill-advised. Menstrual dysfunction and psychosexual difficulties increase with age and may exacerbate the side-effects of some methods of contraception. The long-term risks of combined hormonal contraception, particularly cardiovascular disease, become more pertinent to women whose natural risk of disease increases with age. Patterns of sexual activity and contraceptive use change with age. The advantages and disadvantages of currently available methods of contraception are difficult to quantify, and the choice of method is very much a matter for individual concern. The increasing prevalence of HRT may complicate matters for some women who are unsure for how long to continue using contraception. Contraceptives of the future may be designed to improve the reproductive health of all women, particularly those approaching the menopause.

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ORIGINAL RESEARCH ARTICLE

ELSEVIER

# Incidence of Ovulation in Perimenopausal Women Before and During Hormone Replacement Therapy

Ailsa E. Gebbie, Anna Glasier, and Vicky Sweeting

*Once hormone replacement therapy (HRT) has been commenced, it becomes extremely difficult to advise women approaching the menopause on the need for contraception. In this study of twenty women, neither the regularity of their pre-existing menstrual cycle nor a random FSH concentration predicted the likelihood of subsequent ovulation whilst taking HRT. HRT is not reliably contraceptive and women commencing HRT whilst still menstruating spontaneously must be advised on the need for additional contraception.* CONTRACEPTION 1995;52:221–222

KEY WORDS: ovulation, hormone replacement therapy, contraception, perimenopause

## Introduction

Women become less fertile as they approach the menopause. There is nevertheless still the potential for conception if ovulation occurs. Normal practice is to advise women to continue to use contraception for one year following cessation of menstruation if this happens at age 50 years or above, and for two years if menses stop before 50 years. Many women experience symptoms that they attribute to the menopause while still menstruating and they frequently request and commonly receive hormone replacement therapy (HRT). The prescribing of HRT is likely to increase further as there is growing awareness of the favourable effects of HRT, particularly on postmenopausal osteoporosis and coronary artery disease.[1] There is very little information on the contraceptive efficacy of HRT[2] and many doctors are unsure about the need for contraception in perimenopausal women who are using HRT. We report the incidence of ovulation, and by implication therefore the need for contraception, in a group of women before and during oral HRT.

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## Materials and Methods

Twenty women aged between 42 and 52 years attending a community-based menopause clinic complaining of vasomotor symptoms and requesting HRT were recruited to the study. None had contraindications to HRT, had used hormonal contraception within the past year or had a history of anovulatory infertility. On questioning, ten women described having regular cycles while ten were menstruating irregularly with last menstrual periods ranging from one week to ten months earlier (median 4.6 weeks). Circulating serum FSH concentration was checked randomly prior to commencing the study. The women collected a specimen of early morning urine once per week for eight weeks before and for twelve weeks after starting HRT. Ovulation was monitored by measurement of pregnanediol,[3] the metabolite of progesterone, which is unaffected by the concurrent administration of progestogens in HRT.

All women took Prempak-C 1.25 mg/day (conjugated oestrogens 1.25 mg daily with cyclical norgestrel 150 ug for 12 days out of 28). Urine samples were stored at −4°C and later analysed in batches using in-house ELISA[4] and results are expressed as a ratio of the creatinine concentration to allow for variations in urine output. A pregnanediol concentration of >0.5 mmol/g creatinine was taken as the definition of ovulation. FSH was measured using radioimmunoassay. The results were analysed using the Student's t-test for unpaired observations with log transformed data.

## Results

The women with irregular cycles were significantly older (47.3 years + 1.0 SEM, $p < 0.02$) than those still menstruating regularly (45.5 years + 0.75 SEM) and they had significantly higher ($p < 0.001$) mean FSH concentrations (26.0 + 6.5 SEM (range 3–67) IU/L versus 14.2 + 6.0 SEM (range 3–61) IU/L). FSH concentrations in the two groups are demonstrated in Figure 1.

Prior to starting HRT, ovulation was detected in all

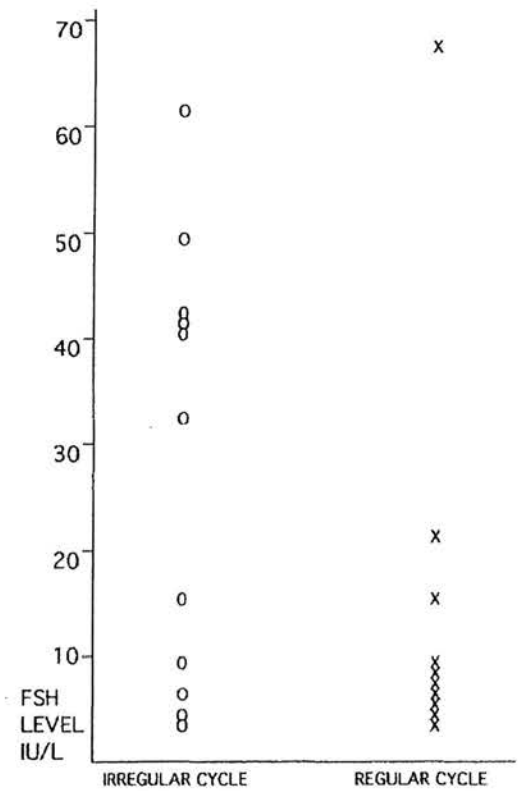


**Figure 1.** FSH concentrations in women with irregular cycles and women with regular cycles.

ten women who had regular menses. Six of them continued to ovulate while taking HRT.

Prior to starting HRT, ovulation was detected in four of the ten women with irregular cycles. Three of these women subsequently had anovulatory cycles whilst taking HRT. Of the six women with irregular cycles who failed to ovulate during monitoring before HRT, three resumed ovulation during treatment.

## Discussion

This small study demonstrates that the oral administration of Prempak-C does not reliably inhibit ovulation even at the higher of the two available doses. Although pregnancy is uncommon in women over 45 years, when it does occur it is associated with increased perinatal mortality, maternal morbidity and a well recognised increase in fetal chromosomal abnormalities. The pregnancy may well be catastrophic psychologically and socially to the woman concerned. Although in our study women over the age of 45 years were more likely to have irregular anovulatory cycles, ovarian activity fluctuated and spells of anovulation were followed by spells of ovulation, clearly putting these women at some risk of pregnancy.

Some of the symptoms experienced by these women may in fact be unrelated to the menopause and could be related to life stresses and the premenstrual syndrome. Use of low-dose, combined oral contraception in healthy, low risk women in this age group can offer reliable contraception and will also relieve many of the symptoms experienced by these women.

The measurement of FSH either before starting HRT or during a break from hormonal contraception is widely used to diagnose the menopause and sometimes is the basis for advising women about the need for contraception. From our study, it is clear that random FSH measurements are variable and that an elevated FSH does not necessarily mean that ovulation is not occurring or will not occur in the future. One woman had an FSH concentration of 67 IU/L before entering the study, yet she ovulated in the next cycle with urinary pregnanediol measurements, suggesting entirely normal ovarian function.

Clearly, neither age, regularity of menstrual cycles nor the measurement of FSH can reliably be used to predict the need for contraception in perimenopausal women using HRT. To be absolutely safe, it is probably still best to advise women taking HRT to continue to use some form of contraception until one or two years after their last spontaneous menstrual period. This study highlights an important clinical area and further research on larger numbers of women is definitely indicated.

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# Handbook of Family Planning and Reproductive Healthcare

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7

# Sterilization

*Anna Glasier*



It has been estimated that worldwide more than 150 million women have chosen sterilization as their method of contraception. Vasectomy is becoming increasingly acceptable and is used by over 50 million couples throughout the world, the majority of whom live in developing countries.

In Britain, almost 30% of all couples, and almost 50% of those over 40, are using either female or male sterilization as their method of contraception.

## FEMALE STERILIZATION

Female sterilization usually involves blocking both fallopian tubes which can be reached either by laparotomy or mini-laparotomy or, more commonly, laparoscopy. In their recent evidence-based guidelines, the Royal College of Obstetricians and Gynaecologists (RCOG 1999) in the UK has recommended laparoscopy, wherever possible as a day case, as the procedure of choice.

Sterilization may also be achieved by the removal of both tubes (salpingectomy) or by hysterectomy, if either procedure is indicated by the presence of gynaecological disease such as hydrosalpinx or fibroids.

### Laparoscopy

General anaesthesia (GA) is normally used, although spinal or local anaesthesia (LA) is more common in the USA and in developing countries where skilled anaesthetists may not be available. A pneumoperitoneum is created by the insufflation of nitrous oxide or carbon dioxide into the peritoneal

cavity. Through a small subumbilical incision, a trochar and cannula are introduced into the gas-filled abdomen and the trochar replaced by the laparoscope (Fig. 7.1). With a fibre-optic light source connected, the pelvic organs are inspected. Operating forceps are introduced through a second cannula inserted either suprapubically or in the iliac fossa. Sterilization is performed either by diathermy or the application of clips or rings to both tubes (see below). After the release of gas from the peritoneal cavity, the instruments are withdrawn and the skin incisions closed with sutures (absorbable or non-absorbable), clips or staples.

## Mini-laparotomy

Laparotomy using a small (3–5 cm) suprapubic incision avoids the need for sophisticated equipment and can be done almost as quickly as laparoscopic sterilization. The uterus is manipulated vaginally to bring the fallopian tubes to the level of the incision. The tubes are delivered through the incision and rings or clips applied. Alternatively, the tubes may be ligated using a variety of methods, most of which involve excision of a small portion of tube.

In the UK, mini-laparotomy is most commonly used when sterilization is performed immediately postpartum as at that time the uterus is large, the pelvis very vascular, and the risks of laparoscopy are increased.

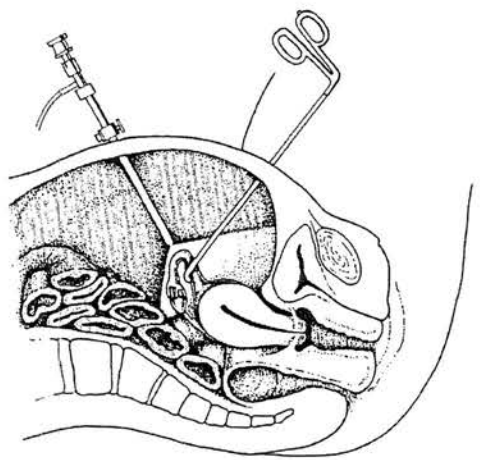

**Figure 7.1**
Laparoscopy.



Mini-laparotomy may be performed as a day-case procedure but many surgeons prefer the patient to stay in hospital overnight.

## Techniques

Whatever the approach, the fallopian tubes may be blocked or divided in a number of ways.

### *Clips*

A variety of clips have been designed for tubal occlusion. The clips destroy a much smaller length of tube (Fig. 7.2) and thus allow easier reversal, but special care must be taken to ensure that the whole width of the tube is occluded – some surgeons routinely apply two clips to each tube. Those most commonly used in the UK are probably the Hulka–Clemens clip (Fig. 7.3A) made of stainless steel and a polycarbonate, and the smaller Filshie clip (Fig. 7.3B) made of titanium lined with silicone rubber.

### *Falope ring*

The ring is made of silicone rubber and, using a specially designed applicator, is placed over a loop of tube (Fig. 7.4). It destroys 2–3 cm of tube and may be difficult to apply if the tube is thick or fibrotic. Ischaemia of the loop causes significant postoperative pain. The application of local anaesthetic to the tube at the time of the procedure (in addition to traditional postoperative pain relief) has been shown to be of benefit.

### *Diathermy*

One or more areas of the tube are cauterized by diathermy (Fig. 7.5). Unipolar diathermy has been replaced by the potentially safer technique of bipolar diathermy which allows only the tissue held between the jaws of the forceps to be cauterized. Local burns may still occur as the temperature of the cauterized tube may reach 300°C–400°C and thus can cause thermal injury if allowed to touch adjacent structures. Failure to cauterize all the layers of the tube results in a relatively high failure rate and cautery near the cornual portion of the tube is thought to increase the risk of ectopic pregnancy. The RCOG guidelines recommend diathermy only if for some reason mechanical methods of occlusion are difficult to apply.

### *Laser*

Recent advances in laser technology have led to attempts at division of the tubes by laser vaporization. The carbon dioxide laser divides the tube very cleanly, which ironically may allow a high incidence of spontaneous tubal

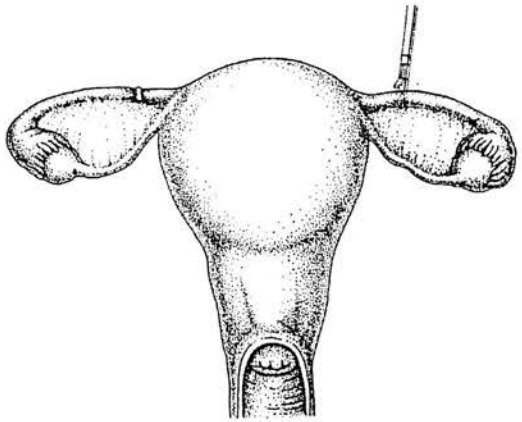

Figure 7.2
Application of clips.

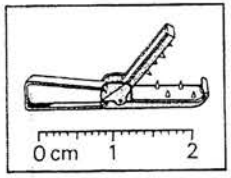


Figure 7.3
(A) Hulka–Clemens clip.

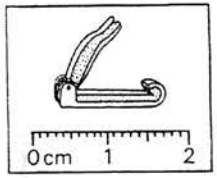


Figure. 7.3
(B) Filshie clip.

recanalization, and therefore failure. The Nd:Yag laser, although probably more effective, is extremely expensive.

*Non-surgical methods*

A number of chemical agents have been tested for their ability to occlude the fallopian tube when instilled into the tube either directly or via the





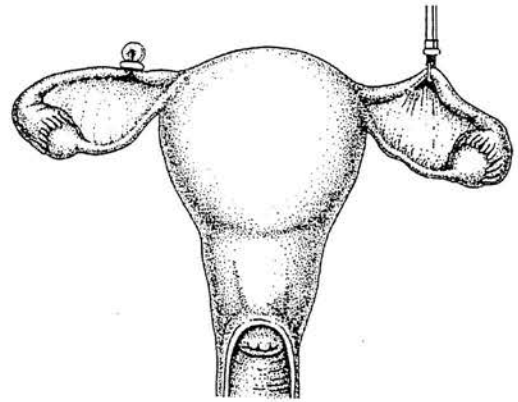

Figure 7.4
Application of falope rings.

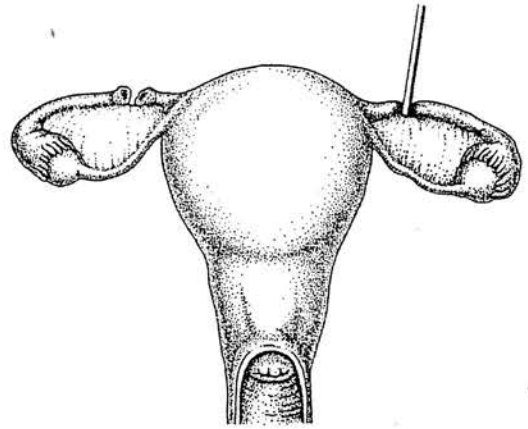

Figure. 7.5
Diathermy coagulation of fallopian tubes.

uterus. The best known is quinacrine. Quinacrine pellets are inserted into the uterine cavity through the cervical canal via a modified intrauterine device (IUD) inserter. Two insertions are made 1 month apart causing inflammation, fibrosis and occlusion of the intramural segment of the tube. Efficacy can be increased by adding adjuvants such as antiprostaglandins or by increasing the number of quinacrine insertions. The method is cheaper

than surgical sterilization, and can be performed by non-medical personnel. A trial of the method in Vietnam reported a failure rate of 2.6% after 1 year (Hieu et al 1993). However, the Indian Medical Research Council in 1998 abandoned their trial because of very high failure rates and the use of quinacrine for female sterilization has now been banned in India. Interest in non-surgical methods was revived in the latter half of 1999 and studies of the toxicology of quinacrine are underway.

## Clinical management

*Examination*

1. General physical examination should identify any risks for anaesthesia and any factors which might contraindicate or complicate the operation, such as previous abdominal operations or gross obesity.
2. Pelvic examination, to exclude existing pathology such as ovarian cyst or fibroids, is mandatory and a cervical smear should be taken if indicated.

*Timing of operation and preoperative advice*

1. Sterilization can be performed at any time in the menstrual cycle. A pregnancy test must be performed preoperatively if a woman has a late period or thinks she might be pregnant.
2. Routine curettage at the time of the procedure in order to prevent luteal phase pregnancy is not recommended and would risk contravening the Abortion Act.
3. Reversible contraception should be continued until the operation. It is not necessary to stop the combined pill before sterilization as the risk of thromboembolic complications is negligible. If an IUD is in situ, it should be removed, unless the operation is being done at mid-cycle and intercourse has taken place within the previous few days.
4. Immediate postpartum or post-abortion sterilization is more likely to be regretted and, as discussed earlier, carries more risks.
5. It is not necessary to shave the pubic area or abdomen before laparoscopy or mini-laparotomy.

*Postoperative advice*

1. Skin incisions closed with absorbable sutures require no further treatment. If clips or non-absorbable sutures are used they will be removed before leaving hospital, or arrangements made to have this done at home. The wounds will usually heal within 10 days.
2. Slight bruising and discomfort may sometimes be experienced around the wounds for a few days.



3. Gas remaining in the peritoneal cavity often causes abdominal discomfort or shoulder pain for 24 to 48 hours.
4. Most women return to work within 48 hours of sterilization.
5. A mini-laparotomy wound takes a few days longer to heal and heavy lifting should be avoided for about 3 weeks.
6. Female sterilization is effective immediately and sexual activity may be resumed when the couple feel like it.

It is helpful to provide a leaflet containing a summary of this information (Appendix 7.1).

*Follow-up*

The resumption of menses may be delayed in women who have stopped using the combined pill. However, if the patient is amenorrhoeic, pregnancy should always be excluded as she may have already been pregnant at the time of sterilization. If she was previously using an IUD, check that it has been removed; occasionally it gets forgotten!

## Complications

*Immediate complications*

1. The operation carries a small operative mortality – < 8 per 100 000 operations.
2. Vascular damage or damage to bowel or other internal organs may occur during the procedure and is usually recognized at the time of operation. Women should therefore be made aware of the rare need for a laparotomy and consequent longer stay in hospital. Unrecognized bowel damage should be suspected in any patient with unexplained pain, pyrexia and abdominal rigidity occurring within the first 2 weeks of sterilization. Such cases should be referred to hospital urgently.
3. Thromboembolic disease is rare, but is more likely if the procedure is done immediately postpartum.
4. Infection or oozing from the wound does occasionally occur and can be managed symptomatically.

*Late complications*

1. ***Menstrual bleeding patterns.*** Female sterilization does not alter ovarian activity or menstruation (Gentile et al 1998). Women who stop using the combined pill, however, will almost certainly notice that their periods become heavier, perhaps more painful and less predictable, and should be warned of this. In contrast, women whose previous method of

contraception was an IUD will notice an improvement in their bleeding patterns. Despite this there have been a number of studies which have demonstrated an increased incidence of hysterectomy among women who have been sterilized (Hillis et al 1998). Bearing in mind the inevitable changes in menstrual bleeding patterns associated with advancing age and with stopping the combined pill (the most commonly used method of reversible contraception), it may be that women who have been sterilized are more likely to seek hysterectomy, or more willing to accept it, if they are already incapable of further childbearing.

2. The term ***post-tubal sterilization syndrome*** was coined to describe a variety of symptoms that have been reported after sterilization and which women may attribute to the procedure. These symptoms include abdominal pain, dyspareunia, exacerbation of premenstrual syndrome or dysmenorrhoea and emotional and psychosexual problems. Laparoscopy fails to demonstrate any pathology. A recent review of the literature (Gentile et al 1998) concluded that sterilization is not associated with an increased risk of these problems except among women sterilized before the age of 30 in whom the symptoms may sometimes be a manifestation of regret.

3. ***Bowel obstruction*** from adhesions is a very rare complication.

4. ***Ectopic pregnancy*** has been reported in up to 50% of failures following cautery and in 4% following mechanical occlusive methods. A large collaborative study undertaken in the USA and involving over 10 000 women was reported in 1996 (Peterson et al 1996). The 10-year cumulative probability of ectopic pregnancy was 7.3 per 1000 procedures.

Women should be advised that **if they miss a period and have symptoms of pregnancy they should seek medical advice urgently**.

5. Several studies have suggested that tubal sterilization may reduce the risk of ovarian cancer. In one large American study, the hazard ratio was 0.64 (Miracle-McMahill et al 1997). The reason for this association is not at all clear.

## VASECTOMY

### Techniques

Vasectomy involves the division or occlusion of the vas deferens to prevent the passage of sperm. It can be performed under LA or GA. A variety of techniques for vas occlusion is available but the principle is the same in all of them.

#### *Division and ligation*

The vas is palpated through the skin of the upper scrotum and fixed either instrumentally or between the fingers and thumb. The vas within its fascial sheath is exposed through a small skin incision, the fascia is opened longitudinally and the vas ligated and divided (Figs 7.6 and 7.7) or occluded with clips or by diathermy. Interposing the fascial sheath between the cut ends of the vas is thought to increase the effectiveness of the procedure. The sheath and scrotal skin are closed separately. The vas may be approached either by a single midline incision or by two incisions, one on each side. Variations in technique include:



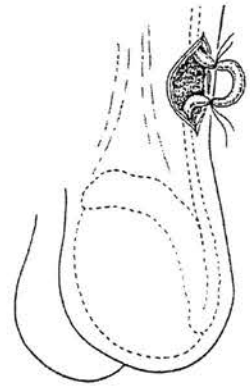

**Figure 7.6**
Vas ligated.

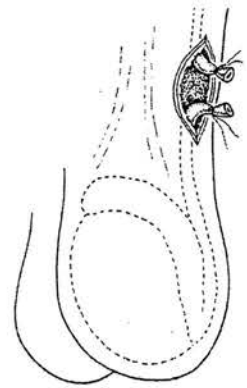

**Figure 7.7**
Vas divided.

1. *Excising a small portion of vas*. It is unlikely that this increases effectiveness unless at least 4 cm of vas is excised and excision makes reversal more difficult. It does however allow the portion of vas to be examined histologically which may help in subsequent cases of litigation but also increases the expense of the procedure.
2. *Looping* each cut end of vas back on itself.
3. *Occlusion using a small silver clip*.
4. *Occlusion using unipolar diathermy* with a specifically designed probe which is passed 1 cm proximally and distally down the divided vas, coagulating the tissue for 3 to 4 seconds until the muscle becomes opaque.
5. *The 'no-scalpel vasectomy' (NSV)*, developed in China in 1974 and now quite widely used, makes use of specially designed instruments for isolating and delivering the vas through the scrotal skin and substitutes a small puncture for the skin incision. Any of the standard methods of occlusion may be used. NSV is quick and is associated with a lower incidence of infection and haematoma. A comparison between NSV and conventional vasectomy in Thailand reported a complication rate of 0.4% compared with 3.1% (Nirapathpongporn et al 1990). Training in the technique can be arranged through the Association for Voluntary Surgical Contraception in New York.
6. *Open-ended vasectomy* – the vas can simply be divided and the cut ends left open. This technique is seldom used as it almost certainly increases failure rates but it does facilitate reversal.
7. *Non-surgical techniques* – percutaneous injection of sclerosing agents such as polyurethane elastomers or occlusive substances such as silicone is being used in China. The technique avoids any skin incision and furthermore the silicone plug is said to be easily removed and pregnancy rates of 100% up to 5 years after vasectomy reversal have been claimed.

No large randomized controlled studies have been done to determine whether one method is any more effective than the other and efficacy probably depends most on the experience of the surgeon.

## Clinical management

### *Assessment*

In addition to the points covered in counselling (pp **191–192**), a history should be taken to exclude any factors which may complicate the operation and which may determine whether LA or GA should be used. These should include:

1. A history of previous genital or inguinal surgery, e.g. orchidopexy.
2. A history of reaction to LA or contraindications to GA (including fear or extreme anxiety).



### *Examination*

In some family planning clinics, where vasectomy is done under LA, the man is counselled by a nurse or doctor and not seen by the surgeon until the time of operation. In this case it is good practice to examine the man prior to recommending him for vasectomy. It is annoying for the patient and a waste of operating time if a problem which precludes vasectomy under LA is not discovered until the patient is being prepared for surgery.

### *Timing of operation*

Some surgeons refuse to perform a vasectomy on men whose wives are pregnant and insist that the operation is delayed until after the safe delivery of a healthy baby. While this would seem sensible to most clinicians, some couples see pregnancy as an extremely convenient time during which the vasectomy can become effective. Each couple should be considered individually in respect of timing of the operation.

### *Preoperative and postoperative advice: follow-up*

1. The patient is usually asked to shave the upper scrotum himself before he presents for operation – this saves both time and embarrassment.
2. He is advised to wear underpants which give good scrotal support for a few days after the procedure.
3. Most men return to work the following day but the risk of haematoma formation is probably reduced if strenuous physical exercise is avoided for 3 or 4 days.
4. It **must** be made clear that it takes some time for remaining sperm to disappear from the distal portion of the vas and that an alternative method of contraception **must** be used until there is azoospermia. The rate at which azoospermia is achieved depends on the frequency of ejaculation. In developing countries where laboratory facilities for examining seminal fluid do not exist, couples are advised to use other contraception until after 20 ejaculations. In the UK, seminal fluid is examined after 12 and 16 weeks and, if sperm are still present, usually monthly thereafter. Not until two consecutive negative samples have been confirmed can the vasectomy be considered to be complete. Instructions for the collection of specimens and their delivery to the laboratory should be given to the patient who should be informed once the vasectomy is complete.
5. Men who experience complications or in whom vasectomy fails seem to be particularly ready to sue. In order to avoid successful litigation, it is imperative that counselling for vasectomy is clear and detailed and covers every eventuality. We have a checklist which counsellors tick as they cover all the points in the discussion with the couple. In Edinburgh, a detailed

information leaflet (Appendix 7.2) is sent out with the first appointment informing the couple about complications and the failure rate before they attend for counselling. They are asked to sign a form stating that they have read and understood the information sheet in addition to the standard form consenting to operation.

## Complications

### *Immediate*

1. ***Bruising and haematoma***. Almost everyone will experience scrotal bruising but in 1–2% of men postoperative bleeding will be sufficient to cause a haematoma. Local support and analgesia are usually adequate treatment but a small number of men will require admission to hospital for drainage of the haematoma.
2. ***Wound infection*** occurs in up to 5% of men and may need treatment with antibiotics.
3. ***Failure*** – up to 2% of men fail to achieve azoospermia. If sperm continue to appear in the ejaculate for months, the vasectomy can be re-done. The timing of a 're-do' or exploration is a matter for discussion between the patient and surgeon. The continued presence of sperm may be due to infrequent ejaculation but if this does not appear to be the case and if many sperm are present, it seems a little hard to ask the patient to provide specimens month after month before admitting defeat.

### *Late*

1. ***Sperm granulomas*** – small lumps may form at the cut ends of the vas as a result of a local inflammatory response to leaked sperm. These may be painful and palpable and pain can persist for years. Excision usually solves the problem. Sperm granulomas may also physically unite the cut ends of the vas and increase the chance of failure.
2. ***Chronic intrascrotal pain and discomfort*** (post-vasectomy syndrome) – some men complain of a dull ache in the scrotum which may be exacerbated by sexual excitement and ejaculation. The symptoms are probably due to distension and granuloma formation in the epididymis and vas deferens. Pain may also result from scar tissue forming around small nerves. Chronic pain associated with progressive induration, tubular distension and granuloma formation in the epididymis may require excision of the epididymis and obstructed vas deferens.
3. ***Late recanalization*** – failure can occur up to 10 years after vasectomy despite two negative samples of seminal fluid following the procedure. It is rare (1 in 1000) but pregnancy as a result of late recanalization is always a sensitive issue. It is not tactful to cast any doubt on the paternity of the pregnancy. Seminal analysis can be offered but if no sperm are seen in the ejaculate this may cause major domestic problems for the couple concerned. Every case must be handled individually but it is sometimes best simply to offer a re-do without semen analysis.
4. ***Antisperm antibodies*** – after vasectomy, most men develop detectable concentrations of autoantibodies presumably in response to leakage of sperm. Their presence may compromise fertility if reversal is sought.
5. ***Cardiovascular, endocrine and autoimmune disease*** – concerns about a possible link between vasectomy and cardiovascular disease were raised in the 1970s following the observation that vasectomy increased atherosclerosis in rhesus monkeys. It was suggested that this may be attributable to increased levels of auto-antibodies which might alter the risk of autoimmune disease in general, including joint disease and multiple sclerosis. Several large studies, including a cohort study in the USA of over 10 000 vasectomized men, have failed to substantiate increased rates of 98 diseases and in fact suggested that vasectomy was associated with a lower death rate (Massey et al 1984). See McDonald (1997) for a useful review of the long-term effects of vasectomy on health.
6. ***Cancer*** – two epidemiological studies from the USA and Scotland (Strader et al 1988, Cale et al 1990) suggested an increased risk of testicular cancer following vasectomy. This observation has not been substantiated by later research. A large study of over 73 000 Danish men (Moller et al 1994) concluded that testicular cancer is no more common in men who have been vasectomized than in other men. A number of large epidemiological studies from the USA have also suggested an increased risk of prostate cancer following vasectomy (McDonald 1997). At a meeting in 1991, the World Health Organization (WHO) reviewed biological and epidemiological evidence and concluded that there was no known biological mechanism to account for any association and that any causal relationship between vasectomy and prostate cancer was unlikely. The National Institute of Health in the USA in 1993 endorsed the WHO conclusions and recommended that there was insufficient basis to change policies regarding vasectomy. A review of the literature in 1998 by Peterson and Howards concluded that vasectomy is unlikely to be a major risk factor for prostate cancer.

## Indications

1. Couples who are absolutely certain that their family is complete.
2. Individuals or couples who choose to have no children.
3. When one partner:
   a. carries a significant risk of transmitting an inherited disorder
   b. suffers from chronic ill-health which would (in the case of the woman) contraindicate pregnancy or affect the couple's ability to bring up children.

In the last two instances, it is sensible to sterilize the affected partner.

practitioner and the surgeon does not meet the patient until the operation. Vasectomy is often done under LA in a clinic setting or in the general practitioner's surgery. In some large family planning clinics, specially trained nurses do the counselling and only seek a medical opinion if there are contraindications, doubts or clinical problems. Sessionally employed surgeons operate on men who have been counselled by someone else. Locally agreed protocols should protect the surgeon from being faced with a patient he/she would prefer not to sterilize for whatever reason.

## Effectiveness

Failure of female sterilization varies according to both the method used and the experience of the surgeon. The U.S. Collaborative Review of Sterilization demonstrated higher failure rates than had previously been reported. It has been suggested that the figures are misleading because they include a great many procedures performed by junior doctors in training. This, of course, is the reality in the UK. The 10-year cumulative pregnancy rate per thousand women was highest for spring clips at 36.5. The rates for bipolar diathermy were 24.8/1000 and for falope rings 17.7/1000. Cumulative pregnancy rates varied not only by the method of tubal occlusion but also by age at the time of sterilization with significantly higher failure rates among women aged 18–27 than those aged 34–44. The simplest way to explain these statistics is to tell women that they have a 1 in 200 chance of getting pregnant at some time after being sterilized.

Vasectomy is generally accepted as being more effective than female sterilization. In the Oxford/FPA study, Vessey et al (1982) reported a failure rate of 0.02 per HWY after vasectomy (1 in 2000).

The RCOG has recommended that a national register of sterilization failures would facilitate both national and local audit and allow couples to be given more accurate information about the procedures.

## Reversibility

Couples should be advised that sterilization is intended to be permanent. Despite careful counselling, however, it is inevitable that a few couples will request reversal of their sterilization. This is most likely to happen when the marriage breaks down and one or other partner starts a new relationship. Although as many as 10% of couples regret being sterilized, only 1% of these will request reversal. Counselling for sterilization should include information on the success rates associated with reversal.

Reversal of female sterilization is more likely to be successful after occlusion with clips which have been applied to the isthmic portion of the tube since only a small section of tube will have been damaged. Patients should realize that reversal involves laparotomy, does not always work (microsurgical techniques are associated with around 70% success) and carries a significant risk of ectopic pregnancy (up to 5%). Reversal is unlikely to be available on the NHS in many parts of the UK.



Reversal of vasectomy is technically feasible in many cases with patency rates of almost 90% being reported in some series. Pregnancy rates are much less (up to 60%) perhaps as a result of the presence of anti-sperm antibodies.

Some laboratories now offer a sperm banking service to men prior to vasectomy. The availability of such services complicates counselling since the concept seems to contradict the advice that a couple should not consider vasectomy unless they are absolutely certain they want no more children.

## Risks/benefits

Although sterilization operations do carry small but significant risks, the overall benefits in terms of effectiveness and convenience tend to outweigh these in well-motivated and adequately counselled couples. In a couple who have completed their family, the procedure avoids the need for continued motivation in contraceptive usage and the long-term side effects of effective reversible methods, such as the combined pill and IUD.



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# Appendix 7.1

## STERILIZATION OF THE FEMALE BY LAPAROSCOPY

For a pregnancy to start, an egg must combine with a sperm. This usually takes place in one of the fallopian tubes which join the ovaries to the womb. All methods of female sterilization block the tubes.

The operation we intend to carry out is called laparoscopy. A short general anaesthetic is required. Through a one-inch-long cut below the navel (tummy button), an instrument is passed through the abdominal wall. This allows careful inspection of the womb, tubes and ovaries. If they appear normal, another small instrument is passed through a separate, even smaller incision. This allows the tubes to be blocked with small clips or rings or by means of a very small electric current.

Complications are rare and recovery rapid so that you will usually be allowed home the same day as your operation. Some patients experience pain in the region of the shoulders or vaginal bleeding for some days after the operation, but this need not cause any concern. Very rarely, some unsuspected abnormality will be seen or will occur at the time of operation so that a more major operation is necessary, but it must be emphasized that this is very unusual.

You will be sterile from the time of the operation and it is safe to resume intercourse as soon as you have completely recovered from the operation. Apart from the fact that you can no longer conceive, neither your periods nor your desire for sex will be affected. Once sterilization has been performed, it is permanent and does not require to be repeated after a number of years. Reversal of the operation, which is occasionally requested, is difficult.

Failure of the operation permitting further pregnancy is rare but does occasionally occur. Therefore, if at any time after operation your period is more than 2 weeks late you should consult your family doctor as soon as possible.

# Appendix 7.2

## MALE STERILIZATION

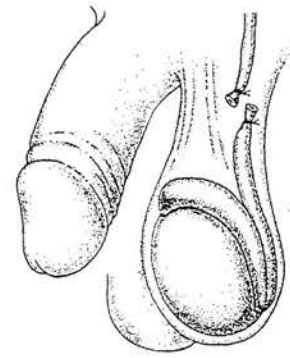
You have expressed an interest in having a vasectomy. You and your partner will be given an appointment to find out more about the procedure before a date is arranged for your operation. This information leaflet tells you about the operation, the effectiveness and side effects. It is designed to give you the facts and to help you decide whether this is to be your chosen method of contraception. It is not meant to sound off-putting but it tells you about the possible complications. You will have the opportunity to discuss the information and to ask questions when you come to the clinic for your vasectomy counselling appointment. All methods of contraception carry some risk and it is up to you to decide which method is most acceptable. We hope that this information sheet will help you in making your decision.

### What is a vasectomy?

A tube called the vas deferens carries sperm from each testis into the penis. Vasectomy is the cutting or blocking of both these tubes to prevent the passage of sperm (see below). The vas are cut just above the testis. Vasectomy does not interfere with the production of seminal fluid so you will not notice any difference in the amount of fluid you produce when you ejaculate – the fluid simply will not contain sperm. The operation is done under local anaesthetic and takes less than half an hour. A small cut is made in the skin in the middle or on each side of the scrotum and the vas which lies just beneath the skin can then be cut or blocked. The skin may be closed with a stitch or tape or simply left to heal without any closure.

### How effective is vasectomy?

Vasectomy is not 100% effective but one of the advantages of the procedure is that its efficacy can be tested. It takes some weeks for all the sperm that remain in the vas (tube) to disappear



Vasectomy

and the rate at which this happens depends on how often you have intercourse. You will be asked to send a specimen of seminal fluid to the laboratory 12 weeks after your operation and again at 16 weeks. In most cases, both samples will be free of sperm and we will let you know that your operation is complete. In some cases, it takes more than 16 weeks for the sperm to clear and you will be asked to continue to send samples every 4 weeks until two consecutive samples are free of sperm. In up to 2% of cases (2 in 100 men), sperm continue to appear and you will be advised to have the vasectomy explored, usually under general anaesthetic in hospital. **Until you have been told that your operation is complete, you or your partner should continue to use another method of contraception.**

In 1 in 1000 cases the vasectomy fails at a later date – the two ends of the vas heal with time and rarely the canal re-opens (so-called 'late recanalization'). If this happens, your partner may become pregnant despite you having had two sperm-free samples and being told that your operation was complete. Late re-canalization may happen some years after you have had your vasectomy. By comparison, sterilization in the female fails in around 3 per 1000 cases.

## Are there any problems?

Complications can be divided into those which might occur immediately after the vasectomy and those which do not occur for some years.

## Immediate complications

All surgical operations carry some risk and vasectomy is no exception but the problems are usually minor.

Between 5 and 10% of men experience minor local problems after the procedure. Once the local anaesthetic has worn off (after about 2 hours), you will probably feel some discomfort which is usually helped by taking a mild painkiller (paracetamol or aspirin). Most men notice a certain amount of swelling and bruising around the operation site which lasts a few days. Sometimes the site can become infected and you may require antibiotics. If you notice persisting pain, swelling or redness you should contact your general practitioner. Occasionally, a moderate amount of bleeding occurs and the blood slowly collects at the base of the scrotum causing a large swelling or haematoma. 1 in 100 men requires hospital treatment for this complication and although this can be a rather frightening event, it does not cause any long-term problems.

## Long-term consequences

In 10–15% of men, leakage of sperm from the cut end of the vas causes some inflammation and occasionally small painful lumps (sperm granulomas) may appear. Very rarely the pain may last for years after a vasectomy but further surgery usually cures the problem.

A large amount of research has been carried out on the long-term effects of vasectomy in order to establish whether the procedure has any effect on general health. While there seems to be no good evidence for any serious long-term effects, a number of studies have raised the possibility of there being a link between prostate cancer and vasectomy.

Cancer of the prostate is relatively common in men although rare below the age of 65. In Scotland about 650 men die from the disease each year compared with about 2700 men dying from lung cancer and about 1300 women who die from breast cancer. The cause of prostate cancer is not known but it is in some way dependent on the male hormone testosterone.

Most cancers are associated with certain risk factors, e.g. men who have worked with some chemicals are much more likely to develop bladder cancer than those who do not. We do not know what risk factors are related to prostate cancer.

Does having a vasectomy increase your chance of later developing cancer of the prostate? A lot of medical research has investigated the possibility of a relationship between vasectomy and prostate cancer. A number of large studies in China and in the USA have suggested that there is no link between vasectomy and the risk of prostate cancer. Indeed, in the Chinese





study, men who had a vasectomy were healthier than those who had not but prostate cancer is rare in Chinese men. Recently, however, two more studies from America have suggested that there may be a link and that 20 years after a vasectomy your risk of developing prostate cancer may be almost double that of men of the same age who have not had a vasectomy. The risk of a man in Scotland developing prostate cancer is around 1 in 2000. If the American studies are correct this means that if you have a vasectomy, your risk increases to 1 in 1000. Cancer of the prostate is a relatively benign condition and although 1 in 25 men aged 74 years will have a tumour of the prostate, the vast majority will live to a ripe old age and die of other causes.

The World Health Organization (WHO) held a meeting of experts in 1991 to discuss the issue. The experts decided that, despite many years of research, there is no known biological reason for vasectomy causing prostate cancer. It is hard to see how vasectomy might affect the risk of prostate cancer. It is more likely that for some reason men who decide to have a vasectomy have some characteristics which also make them more likely to develop prostate cancer although we do not know what these characteristics might be. WHO recommends that more research should be done but that family planning policies should not be changed.

One or two small studies have also suggested a link between vasectomy and testicular cancer. Again there is no obvious physiological basis for such a link and it is possible that men who have recently had a vasectomy may be more likely to examine themselves and so find a lump in the testis.

What does this mean for you? All methods of contraception carry some risk. When you decide on a family planning method you weigh up the risks and benefits for you and your partner. Long-term use of the contraceptive pill carries a small risk for women as does female sterilization. On the whole, whatever the method, using contraception is probably safer than either having a baby or having an abortion. Moreover, apart from the health risks involved, individual couples must consider what an unplanned pregnancy would mean to their lives. While you and your partner have to decide for yourselves whether or not to choose a vasectomy, many couples may consider that the small risk of problems is acceptable when balanced with the benefits of an extremely effective method of contraception.

## Can vasectomy be reversed?

Yes, but reversal is not always successful. It requires an intricate operation and even if the cut ends of the vas are successfully united and sperm can get through, fertility may not be normal. The operation may not be available from the National Health Service so if you were to request reversal you might have to pay for it. You should not have a vasectomy if you think that you might at some time want to have the operation reversed.

## Practical details

This information leaflet is being sent to you before your appointment for counselling. You should expect to be in the clinic for about half an hour for this consultation. It is helpful if your partner accompanies you as she may also have some questions. Unfortunately, we do not have crèche facilities and you may find it difficult to concentrate if you are being distracted by your children so we strongly recommend a baby-sitter if you can find one!

If you decide to go ahead with a vasectomy, you will be given a date for the operation. You should remember to shave the scrotum and the skin around the base of the penis before you come to the clinic. This is best done in the bath the night before the operation.

After the operation you will have a short rest before going home. You will probably be in the clinic for less than 1 hour. You should rest at home for the remainder of the day and will probably find it comfortable to wear either an athletic support (jock strap) or a pair of well-supporting underpants for a couple of days.

Most men return to work the following day but you should avoid lifting heavy weights or doing other heavy manual work for 3 or 4 days. It is not sensible to arrange unavoidable commitments or energetic holidays immediately following the operation.

We hope that you have found this information leaflet helpful. When you come to the clinic you will be asked to sign a copy saying that you have read and understood the information and

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# Laparoscopic sterilisation: opinion and practice among gynaecologists in Scotland

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**Objectives** 1. To produce a list of evidence-based criteria for good quality care relating to female laparoscopic sterilisation. 2. To assess the level of agreement with each criterion among gynaecologists in Scotland. 3. To obtain an overview of current sterilisation practice for comparison with the agreed criteria.

**Design** 1. Agreement with criteria assessed by questionnaire survey; 2. Overview of current practice obtained by questionnaire survey and by casenote review.

**Setting** Scotland.

**Sample** 1. Questionnaire survey: all 132 consultant gynaecologists in NHS practice. 2. casenote review: 988 consecutive women sterilised in 12 representative hospitals.

**Results** The response rate to the questionnaire survey was 94%. A list of 15 evidence-based criteria was produced, covering patient selection, information and counselling, techniques of tubal occlusion and timing of sterilisation. All 15 suggested criteria gained an overall balance of support among responding gynaecologists. Similar impressions of current practice were gained from the questionnaire survey and from the casenote review. Aspects of practice which measured up well to the agreed criteria included: only 6% of women sterilised were younger than 25 years of age; over 85% of casenotes included clear documentation that women had been counselled regarding failure rate and intended permanency; 88% of sterilisations were performed, or directly supervised by, a gynaecologist of consultant or senior registrar status; and only 2% of sterilisations were undertaken in combination with induced abortion. Aspects of practice which compared poorly with the agreed criteria, and for which recommendations for change have been made, included: only 22% of casenotes mentioned that the option of vasectomy had been discussed; only 30% of gynaecologists indicated that they provide locally produced information leaflets as an adjunct to counselling; four methods of tubal occlusion (including unipolar diathermy) were in use; and there were wide variations among hospitals in the use of day-case care, ranging from 19% to 99%.

**Conclusions** A list of criteria for good quality care in relation to sterilisation has been validated by agreement among Scottish gynaecologists. Current practice (as assessed by questionnaire survey and casenote review) has been compared with the criteria and some recommendations for change in practice have been made. Following dissemination of these results and recommendations, re-audit will be undertaken in order to identify any changes.

## INTRODUCTION

Laparoscopic sterilisation is a major component of the Scottish NHS gynaecological workload. Around 7700 such procedures are undertaken annually and comprise almost 10% of total gynaecology inpatient plus day-case discharges (Information and Statistics Division, NHS in Scotland, 1993). Complications and failures of sterilisation are a common cause of litigation against gynaecologists, and there is concern regarding the frequency of requests for reversal; 329 reversals of female sterilisation were performed in Scotland in 1993 (Information and Statistics Division, NHS in Scotland, 1993).

Despite the frequency of sterilisation and the concerns regarding litigation and patient-regret, there are no agreed guidelines within Scotland covering selection of patients, pre-sterilisation counselling or appropriate techniques for tubal occlusion. It was therefore decided to address the topic of female laparoscopic sterilisation within a national audit project, the Gynaecology Audit Project in Scotland. As part of this project the views of gynaecologists

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Table 1. Suggested criteria for good quality care in relation to laparoscopic sterilisation plus references from the literature on which they are based. Where no references are given, the statement summarised the views of the discussion panel.

| Criterion | Supporting references |
|---|---|
| **Patient selection** | |
| 1. In almost all cases, sterilisation should be refused to women under the age of 25 and reversible methods of contraception advised | 2–6 |
| 2. Prior to sterilisation it should be verified, by gynaecological history taking and examination, that a more radical operation is not indicated | — |
| **Patient information and counselling** | |
| 3. Prior to female sterilisation, it should be ascertained that the option of vasectomy has been fully discussed with married/cohabiting couples. | 7, 8, 35 |
| 4. Pre-sterilisation counselling should include discussion of failure rate (including risk of ectopic pregnancy) and complications and should emphasise that the procedure is intended to be permanent. | 34 |
| 5. Pre-sterilisation counselling should include enquiry into any disharmony within the current relationship. | 3–6, 13, 32, 36–38 |
| 6. The fact that the patient has been counselled regarding failure rate, complications and irreversibility should be documented in the case notes as well as appearing on a printed consent form. | 34 |
| 7. Prior to sterilisation, women should be given an information leaflet summarising the various factors covered in the counselling. | — |
| 8. The likelihood of a less acceptable menstrual pattern following sterilisation should be discussed with current users of the contraceptive pill. | 9–12, 39 |
| 9. Women should be advised to continue with their current method of contraception (including the contraceptive pill) until their admission for sterilisation. | — |
| **Techniques for sterilisation** | |
| 10. Filshie clips represent the tubal occlusion technique of choice. | 9, 13–22, 40–44 |
| 11. Except where there are medical, social or geographical contra-indications, laparoscopic sterilisation should be performed as a day-case. | 45, 46 |
| 12. A post-MRCOG gynaecologist should perform, or be present at, all laparoscopic sterilisations and should confirm occlusion of both fallopian tubes. | 34 |
| **Timing of sterilisation** | |
| 13. For almost all patients, sterilisation should be undertaken as an interval procedure rather than in association with pregnancy (ie post- natally or combined with induced abortion). | 13, 18, 23–31, 33, 34 |
| 14. Patients requesting sterilisation in association with pregnancy should be informed that this increases the failure rate at least three-fold. This warning should be documented in the case notes. | 34 |
| 15. On admission for sterilisation, co-existing pregnancy should be excluded by taking a menstrual and contraceptive history. A sensitive pregnancy test should be performed in cases of doubt. | 34 |

about a list of evidence-based criteria for good quality care relating to sterilisation were sought by means of a postal questionnaire survey, and additional questions were asked about current sterilisation practice. Information about current practice in Scotland was obtained by means of casenote review in 12 representative hospitals.

The results of these exercises are presented in this paper and will be disseminated among gynaecologists in Scotland. In due course re-audit will be undertaken in order to identify any changes in practice. The criteria for good quality care discussed here may provide a basis for the development of formal clinical practice guidelines.

## METHODS

A review of contemporary medical literature relating to laparoscopic sterilisation provided the basis for a provisional list of statements, or criteria, regarded as summarising essential elements of good practice. The criteria covered four broad aspects of patient management: *patient selection*, *information and counselling*, *techniques for tubal occlusion* and *timing of sterilisation*. The provisional list of criteria was modified and refined following discussion by a panel of clinicians, comprising three gynaecologists with a special interest in fertility control and three generalists. The final list of 15 criteria with a summary of references from the literature review in support of each is shown in Table 1.

A questionnaire was then designed to assess level of agreement with each criterion. Recipients were asked to indicate their level of agreement with each statement, as representing an important criterion for good quality care, on a five-point scale. The scale was graded *strongly agree*, *agree*, *neither agree nor disagree*, *disagree*, and *strongly disagree*. Other questions addressed aspects of current practice related to the same four broad aspects of care covered by the 15 criteria.

In November 1994 the questionnaire was mailed to all 132 consultant gynaecologists in NHS practice in Scotland at that time. The mailing list was based on names and addresses obtained from the Royal College of Obstetricians and Gynaecologists and updated by telephone enquiry to all 26 gynaecology units in Scotland. A second copy of the questionnaire,

Table 2. Levels of agreement with criteria for good quality care. For each criterion (numbered as in Table 1), the table shows the ranking in importance assigned, the agreement score (on a scale ranging from +100 to −100) and the percentage of consultants who agreed or strongly agreed.

| Rank | Criterion No. | Abbreviated criterion | Agreement score | % agreed |
|---|---|---|---|---|
| 1 | 4 | Content of counselling | +91 | 100 |
| 2 | 6 | Documentation of counselling | +86 | 98 |
| 3 | 9 | Continue contraception pre-sterilisation | +80 | 98 |
| 4 | 15 | Exclude co-existing pregnancy | +78 | 94 |
| 5 | 14 | Document increased failure rate for sterilisation in association with pregnancy | +58 | 83 |
| 6 | 11 | Day-case care | +55 | 82 |
| 7 | 2 | Pre-sterilisation history and examination | +50 | 81 |
| 8 | 13 | Interval procedure rather than concurrent with abortion | +49 | 78 |
| 9 | 3 | Vasectomy discussed | +46 | 72 |
| 10 | 8 | Post-pill altered menstrual pattern | +43 | 76 |
| 11 | 5 | Enquiry into disharmony in relationship | +37 | 67 |
| 12 | 12 | Post-MRCOG gynaecologist present | +36 | 64 |
| 13 | 7 | Information leaflet | +36 | 59 |
| 14 | 10 | Filshie clip: method of choice | +22 | 54 |
| 15 | 1 | Age cutoff of 25 years | +7 | 46 |

with a letter of reminder, was sent to those consultants who did not respond within three weeks. Data from the questionnaires were entered into a database using Paradox (Borland) software on an IBM-compatible PC.

In order to quantify the overall balance of agreement with the suggested criteria, an agreement score was allocated to each criterion. The agreement scores were calculated as previously described[1] by allocating each response of *strongly agree* a score of +2; of *agree* +1; of *neutral* 0; of *disagree* −1 and of *strongly disagree* −2. The scores for each criterion were summed and expressed as a percent of the maximum possible score had all participants *strongly agreed*. Thus, any positive score indicates a balance of agreement, +100 is the maximum possible score and −100 is the minimum possible score.

Twelve hospitals throughout Scotland were recruited into the casenote review audit. These were selected as being representative of Scotland as a whole in terms of teaching/district general, large/small and geographical spread. A casenote review document was designed for the transfer of information relating to the agreed criteria from patients' records. Audit assistants with a medical secretarial background in each hospital received a training session from one of the Research Fellows (V.S./G.C.P.) on transferring information from sample casenotes to the document. Thus, data were collected in a standardised manner in all 12 participating hospitals. Commencing in June 1995, the audit assistants began identifying 100 consecutive cases of laparoscopic sterilisation undertaken in each hospital, completed the casenote review documents and returned them to the project office for computerisation.

## RESULTS

### Response rates

As a result of the two mailings, 124 completed consultant survey questionnaires were received (a response rate of 94%). One consultant indicated that he never performed laparoscopic sterilisation and answered no further questions. Thus, the resulting overview of current opinion and practice is based on the replies of 123 gynaecologists who undertake female sterilisation in the course of their routine NHS practice.

The intention was to review the notes of 100 consecutive patients in each of the 12 participating hospitals. However, in the funded data collection period of approximately four months, fewer than 100 sterilisations were performed in some hospitals. A total of 988 cases were reviewed (mean 82 cases per hospital; range 41 to 100 cases).

### Opinion on suggested criteria for good quality care

Table 2 summarises all 15 criteria arranged according to agreement scores. The scores represent an attempt to indicate the strength of support for each criterion, giving additional weighting to responses of *strongly agree* or *strongly disagree* rather than simply *agree* or *disagree*; however the level of agreement with each criterion is also shown in terms of the percentage of respondents who *agreed* or *strongly agreed*.

All 15 criteria gained positive agreement scores, indicating a balance of support among consultants. However, the level of support ranged from universal agreement with *"Pre-sterilisation counselling should include discussion of failure rate (including risk of*

*ectopic pregnancy) and complications and should emphasise that the procedure is intended to be permanent"* to a meagre balance of agreement with *"In almost all cases, sterilisation should be refused to women under the age of 25 and reversible methods of contraception advised"*.

## Overview of current practice

### *Patient selection*

Consultants were asked whether or not they adopt an age cutoff below which they would usually refuse sterilisation. Only 27 (22%) indicated that they do so; the most popular minimum age selected was 25 years (as suggested in the audit criterion), ranging from 16 to 30 years. Among the 988 patients studied in the casenote review, only 56 (6%) were younger than 25 years of age and 280 (28%) were younger than 30. Among individual hospitals the proportion of women sterilised under 25 and under 30 years of age ranged from 2% to 10% and 18% to 43%, respectively.

With regard to adequacy of pre-sterilisation gynaecological history taking and examination, the findings of a pre-operative pelvic examination were documented in only 512 (52%) of casenotes, and the result of a cervical smear within the previous three years was documented in only 613 (62%).

### *Patient information and counselling*

No respondents indicated that they routinely insist on counselling women requesting sterilisation along with their partners, although 29 (24%) would ask the male partner to attend if there were particular medical contraindications to female sterilisation; and 57 (46%) would include the male partner in counselling *"if he happened to be present"*. Thirty-seven individuals (30%) indicated that they never see the male partner. Consultants also were asked if they include discussion of vasectomy in pre-sterilisation counselling and whether for couples in stable, long term relations, they usually advocate vasectomy as the method of choice. Sixty respondents (49%) said they always discuss vasectomy, 52 (42%) in *"selected cases"* and 11 (9%) never do so. Only 25 (20%) said they usually advocate vasectomy as the method of choice.

Despite the universal agreement that women should be fully informed about failure rate, complications and irreversibility, only 37 consultants (30%) indicated that a sterilisation information leaflet produced within their own department was available. A further 34 (28%) indicated that standard leaflets (e.g. Family Planning Association) were available and 52 (42%) said that they do not provide information leaflets.

**Table 3.** Usual method of tubal occlusion used at laparoscopic sterilisation. Values are given as *n* (%).

| Method of occlusion | Reported usual practice* | Actual method used† |
|---|---|---|
| Filshie clip | 73 (59) | 617 (62) |
| Falope ring | 35 (29) | 244 (25) |
| Hulka–Clemens clip | 9 (7) | 85 (9) |
| Diathermy methods | 6 (5) | 31 (3) |
| Unclassified | — | 11 (1) |
| TOTAL | 123 (100) | 988 (100) |

*$n$ = 123 gynaecologists responding to questionnaire survey.
†$n$ = 988 cases of laparoscopic sterilisation reviewed.

Results from the casenote review exercise relating to documented counselling mirrored those of the questionnaire survey. Discussion of the option of vasectomy was documented in only 148 cases (15%). However, formal documentation in addition to information on the printed consent form relating to irreversibility and failure rate was found in over 86% of casenotes, although increased risk of ectopic pregnancy among failures was mentioned in only 59%. Evidence of any enquiry into the stability of the current relationship was found in only 45% of casenotes.

### *Techniques for sterilisation*

Consultants were asked which method of tubal occlusion they use most often. Responses are summarised in Table 3. Over half of respondents usually use the Filshie clip with the Falope ring the next most popular method. Of 105 consultants who ever use a clip method of sterilisation, 17 (16%) apply two clips to each tube as a routine. Most of the others (78, 74%) occasionally use two clips when accurate placement of the first clip is in doubt.

The methods of tubal occlusion used in the 988 sterilisations reviewed are also summarised in Table 3. Among the 702 sterilisations where clip methods were employed, more than two clips were applied in 34% of cases. Among individual hospitals the rates of applying more than two clips ranged from 1% to 96%, reflecting the variations in consultants' reported practice.

The vast majority of respondents (104, 84%) indicated that they routinely treat sterilisation as a day case procedure in the absence of medical, social or geographical contraindications. Among the 988 patients reviewed, 714 (72%) were managed as day cases. Of the remainder, 180 women (18%) stayed one night, 81 (8%) stayed two nights and the others for variable, longer periods. Among individual hospitals, day case care rates ranged from 99% down to

19%. These variations were not entirely explicable on geographical grounds as the two hospitals with the lowest utilisation of day case care (19% and 40%) are both located in the central belt of Scotland.

Overall, 738 (75%) of the 988 sterilisations reviewed were performed by a consultant or senior registrar, and it was evident from the operation note that a further 127 procedures (13%) had been directly supervised by a gynaecologist of these grades. Among the 12 individual hospitals studied, the percentage of sterilisations performed, or directly supervised, by a gynaecologist of consultant or senior registrar status ranged from 76% to 100%.

*Timing of sterilisation*

One hundred and eight consultants answered a question about their usual policy for women requesting both induced abortion and sterilisation; the remaining 15 respondents indicated that they do not perform abortions. Of these 108, 30 (28%) would usually perform the two procedures concurrently whereas 78 (72%) would arrange interval sterilisation at least six weeks after abortion. In practice, among the 988 sterilisations reviewed only 17 (2%) were undertaken as combined procedures with induced abortion.

## DISCUSSION

The questionnaire provided an informative overview of current opinion and practice in relation to laparoscopic sterilisation among gynaecologists in Scotland. A list of evidence-based criteria for good quality care has been validated by an overall balance of agreement among participating clinicians and was adopted as the basis of standards for the casenote review audit. In due course, the criteria may also serve as a foundation for the development of a national clinical practice guideline.

The first suggested criterion that in general women younger than 25 years of age should be advised against sterilisation is based on evidence that younger women have a higher incidence of post-sterilisation regret and of request for reversal[2,6]. In a study of some 6000 post-sterilisation patients Wilcox *et al.*[5] found that those who were younger than 30 years at the time of sterilisation were twice as likely to seek information on tubal reanastamosis as those aged 30 to 34. In view of this evidence, and the fact that the number of reversals of sterilisation undertaken annually in Scotland amount to around 5% of the total number of sterilisations (Information and Statistics Division, NHS in Scotland, 1993), it is disappointing that this criterion was the least strongly supported of the 15 suggested.

Criterion 3 suggests that all couples requesting sterilisation should be fully counselled about the option of vasectomy on the basis that this procedure is safer, cheaper and no less effective than female sterilisation[7,8]. Again, it is perhaps disappointing that no gynaecologists insist on counselling pre-sterilisation patients along with their partners and that only a fifth regard vasectomy as the method of choice for most couples.

Reviews of failure rates associated with different methods of tubal occlusion suggest that diathermy carries the lowest overall failure rate (around 2–3 per 1000), whereas Falope rings and clip methods carry a somewhat higher failure rate of around 4 per 1000[13]. However the apparent advantage of tubal diathermy is counterbalanced by the high incidence of ectopic pregnancies among diathermy failures. Ectopic rates of over 50% are reported among pregnancies following tubal diathermy, whereas ring and clip method failures are associated with ectopic rates of less than 5%[13]. Another major drawback of diathermy sterilisation is the potential for serious intra-operative complications, principally bowel burns which may result in the need for bowel resection or even in death[9,14–17]. There seems to be little to choose between ring and clip methods of tubal occlusion in terms of failure and ectopic rates. However, ring methods are associated with more serious intra-operative complications, in the form of tubal avulsion and haemorrhage[9,18,19] and with a higher incidence of peri-operative pain[20]. Another factor to consider when selecting a tubal occlusion technique, particularly for younger women, is the potential for reversibility. Diathermy sterilisation damages up to 5 cm of tube, resulting in a very low potential for successful reversal. Clips damage only around 5 mm of tube, thus providing the optimum chance of success if reversal is required[19]. The project's discussion panel of clinicians therefore agreed that a clip method of tubal occlusion was to be preferred. The Filshie clip was suggested as the tubal occlusion technique of choice on the basis of evidence relating to failure rate, incidence of ectopic pregnancies among failures, peri-operative complications and potential reversibility. The project panel favoured the Filshie rather than the Hulka clip on the basis of one study[21] which directly compared the two, and concluded that the Filshie clip was preferable because its larger capacity facilitated the occlusion of thick tubes and the applicator was easier to use and maintain. The panel strongly supported the views of a British Medical Journal editorial written in 1980[22] which expressed surprise that *"relatively uncontrolled unipolar electrocoagulation is still used, even in some teaching centres in Britain"*. The survey has

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Reviews of failure rates associated with different methods of tubal occlusion suggest that diathermy carries the lowest overall failure rate (around 2–3 per 1000), whereas Falope rings and clip methods carry a somewhat higher failure rate of around 4 per 1000[13]. However the apparent advantage of tubal diathermy is counterbalanced by the high incidence of ectopic pregnancies among diathermy failures. Ectopic rates of over 50% are reported among pregnancies following tubal diathermy, whereas ring and clip method failures are associated with ectopic rates of less than 5%[13]. Another major drawback of diathermy sterilisation is the potential for serious intra-operative complications, principally bowel burns which may result in the need for bowel resection or even in death[9,14–17]. There seems to be little to choose between ring and clip methods of tubal occlusion in terms of failure and ectopic rates. However, ring methods are associated with more serious intra-operative complications, in the form of tubal avulsion and haemorrhage[9,18,19] and with a higher incidence of peri-operative pain[20]. Another factor to consider when selecting a tubal occlusion technique, particularly for younger women, is the potential for reversibility. Diathermy sterilisation damages up to 5 cm of tube, resulting in a very low potential for successful reversal. Clips damage only around 5 mm of tube, thus providing the optimum chance of success if reversal is required[19]. The project's discussion panel of clinicians therefore agreed that a clip method of tubal occlusion was to be preferred. The Filshie clip was suggested as the tubal occlusion technique of choice on the basis of evidence relating to failure rate, incidence of ectopic pregnancies among failures, peri-operative complications and potential reversibility. The project panel favoured the Filshie rather than the Hulka clip on the basis of one study[21] which directly compared the two, and concluded that the Filshie clip was preferable because its larger capacity facilitated the occlusion of thick tubes and the applicator was easier to use and maintain. The panel strongly supported the views of a British Medical Journal editorial written in 1980[22] which expressed surprise that *"relatively uncontrolled unipolar electrocoagulation is still used, even in some teaching centres in Britain"*. The survey has

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ORIGINAL RESEARCH ARTICLE

# Continuation Rates of Long-Acting Methods of Contraception

## *A Comparative Study of Norplant® Implants and Intrauterine Devices*

Diana Fleming, J. Davie, and A. Glasier

*Following adverse widespread publicity in the United Kingdom and the United States, it is commonly believed that discontinuation rates for the contraceptive implants Norplant® in the UK are high.*

*We have compared discontinuation rates between new intrauterine device (IUD) users (253 women) and new Norplant implant users (502 women) over 33 months following the introduction of Norplant implants among a population of women attending the same clinic and counseled in the same manner by the same group of providers. Women choosing the IUD were slightly older and were more likely to be changing their contraceptive method because of dissatisfaction with their current method. Norplant implant users were more likely to have completed their families. Continuation rates for Norplant implants were significantly higher than for IUD at 12, 18, and 24 months after insertion. At 24 months, continuation rates for Norplant implants were 72% compared with rates of 55% for IUD users. Higher continuation rates may be related more to factors associated with the providers than with the users of these two long-acting methods.*
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KEY WORDS: Norplant® implants, intrauterine device, continuation rates

## Introduction

Norplant® implants became available in the United Kingdom in August 1993. Their introduction was accompanied by widespread publicity in the popular press. The pharmaceutical company who marketed Norplant implants had in place a national training program to ensure that a cohort of doctors were competent to insert and remove the rods. Adverse publicity in 1995[1–3] in both the UK and the United States resulted in a number of women requesting removal of implants, which, together with removals for side effects, led to the widespread impression that "everyone was having their implants removed." We audited continuation rates among women who had had Norplant implants inserted in a large community family planning clinic in Edinburgh and demonstrated continuation rates of 84% at 1 year and 80% after 18 months of use.[4] Despite these data and national figures[5] showing similar continuation rates, anecdotally, many medical and nursing staff responsible for delivering contraceptive services in the UK had expressed the view that the Norplant implants launch had been a failure.

We present a study comparing continuation rates among women choosing a copper intrauterine device (also requiring insertion and removal by a doctor), provided in the same clinic setting and during the same time span, with continuation rates among women choosing the Norplant implants.

## Materials and Methods

A retrospective review of the case records was carried out of all women (n = 370) who had had nonhormonal IUD inserted from August 1, 1993, to May 1, 1995, in a large Family Planning clinic in Edinburgh, Scotland. Only first time users of the method (253) were included in the study; all those who had used an IUD in the past were excluded, as the comparison was made with the new users of Norplant implants. There were no other exclusion criteria.

If a patient had not attended the clinic for a follow-up within 1 year of the review, a standard letter of inquiry was sent out to the patient. If the patient failed to reply, a letter was sent to her general practitioner (family doctor) to ascertain whether an IUD was still being used as a method of contraception. If there was no reply following this the GP was con-

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tacted by telephone to establish whether he/she had further information as to the patient's current contraceptive use. Those patients for whom no further information could be collected were recorded as lost to follow-up. Information collected from women who returned their questionnaires included age, parity, date of IUD insertion and removal (if applicable), prior method of contraception, reason for the IUD being requested as a method of contraception, and reasons why removal of the IUD was requested. The same data on new Norplant implants users were collected from the same family planning center, prospectively from August 1, 1993, to May 1, 1995.[4]

Both IUD and Norplant implants users had been counseled before the insertion of the device. Advantages, disadvantages, and suitability of the method were discussed at a general contraceptive clinic. The insertion of the device was undertaken at a second visit in a dedicated IUD or Norplant implants clinic, at which time the suitability for the method was confirmed and counseling reinforced.

Results were analyzed using the $\chi^2$ test for discreet variables. A $p < 0.01$ was considered to be significant.

## Results

From August 1, 1993, to April 30, 1995, 502 women had Norplant implants inserted and were followed-up until the removal of the implant or to April 30, 1996; 45 (9%) of these women were lost to follow-up. A total of 253 new users of nonhormonal IUD were identified, of which 42 (16%) were lost to follow-up.

### *Characteristics of Users*

Women who chose an IUD tended to be slightly older than women choosing Norplant implants (mean age 30.7 vs 27.2 years, respectively). Fifty-four percent of IUD users ($p < 0.001$) were over 30 years of age at the time of insertion compared with 30% of Norplant users. There were no differences in parity or number of liveborn children between women choosing different contraceptive methods. Women who chose Norplant implants were more likely to have been using the combined oral contraceptive pill at the time of choosing their new method than were IUD choosers ($p < 0.001$) who were more likely to be using condoms ($p < 0.01$). The most common reason for choosing Norplant implants was as an alternative to sterilization whereas that for choosing the IUD was because of dissatisfaction with other contraceptive methods.

### *Insertions and Removals*

Figure 1 shows the cumulative number of insertions and removals of the two methods over the 33-month study period. An average of 10.3 (SD 4.0) IUD were inserted each month compared with 24 (SD 13.8) insertions of Norplant implants. Although a higher percentage of IUD were removed during the study, they were removed steadily at an average of 3.2 (SD 1.8) per month. Removals of Norplant implants increased with time with a mean monthly removal rate of 1.4 (SD 2.2) in the first 18 months and a mean of 7.8 (SD 3.8) in the subsequent 15 months.

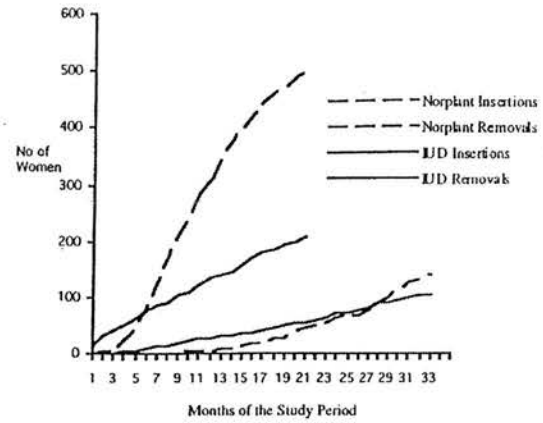


**Figure 1.** Cumulative number of insertions and removals of Norplant implants and nonhormonal IUDs over the 33-month study period (August 1, 1993 to May 1, 1995) in a large family planning clinic in Edinburgh, Scotland.

### *Continuation Rates*

Continuation rates were higher at all time points among users of Norplant implants. At 12 months, continuation rates were 84% for Norplant users compared with 70% for the IUD users, and at 18 months, were 80% for Norplant and 63% for the IUD. By 2 years after insertion, 71.8% of women were continuing to use Norplant implants compared with only 54.6% for IUD users ($p < 0.001$).

### *Reasons for Discontinuation*

More than one reason was often cited for discontinuation of a method. For both methods, the predominant reason for removal was bleeding problems (Table 1). Users of Norplant implants experienced menstrual irregularity, whereas for IUD users menorrhagia was common. In 10 of the 16 cases in which pain was cited as a reason for IUD removal, this was associated with menorrhagia. Other reasons for removal of Norplant implants included mood swings, weight gain, and headaches. Only one woman having the Norplant implants removed cited recent adverse publicity as a reason for removal.

**Table 1.** Reasons for removal of norplant implants (n = 142) and iud (n = 104)

| Reason Removed | Norplant Removals | IUD Removals |
|---|---|---|
| Bleeding problems | 64 | 40 |
| Pain | 6 | 16 |
| Planning pregnancy | 9 | 17 |
| Pregnant | 1* | 4 |
| Expulsion | 0 | 8 |
| Infection | 0 | 7 |
| Preferred sterilization | 6 | 4 |
| Postcoital insertion | 0 | 6† |
| Mood swings | 47 | 0 |
| Weight gain | 23 | 0 |
| Headache | 19 | 0 |
| Acne | 11 | 0 |
| Hair problems | 5 | 0 |
| Relationship ended | 3 | 2 |
| Adverse Publicity | 1 | 0 |

*Pregnancy undiagnosed at time of insertion.
†IUD inserted post coitally, initially planned to continue but changed mind.

## Discussion

Continuation rates among women using Norplant implants were much higher than those for IUD users, which is reassuring to both providers and users particularly as the IUD is regarded as a very useful (although not widely used) method of contraception in the UK. There were no differences in the manner in which the two groups of women were counseled about their choice of method and counseling was undertaken by the same staff in the same clinic. Women using Norplant implants tended to be a little younger than IUD users but, implicit in their choosing between sterilization and Norplant implants, they were perhaps more likely to have completed their families. This is reflected in the higher number of removals among IUD users who were planning another pregnancy.

Although the cost of the chosen method, together with fees for removal or insertion, may play a part in continuation rates in other countries such as the US, this is not the case in the UK where contraception is free to the user. However, providers do pay for the cost of contraception in their clinic budgets and they have become much more cost conscious in recent years. A "trial" of an IUD (at < $16.50 per device) may be regarded as acceptable, whereas a trial of Norplant implants (at $280) would be quite unacceptable. The threshold for insertion and removal of IUD may thus be lower.

Access to removal may also have influenced continuation rates. Although no fees are charged for either insertion or removal of either method, whereas most doctors are capable of removing an IUD, only a small number have been trained to remove the Norplant implants. A woman wishing to have her IUD removed can be seen by her family doctor or by a doctor at a family planning clinic. For Norplant implants users, removal requires a visit to one particular clinic that may be much less geographically convenient, thus encouraging women to postpone removal for a little longer. However, easy access to the implant clinic by telephone, by self-referral, or at the request of her general practitioner was offered at the time of insertion. Assurance was given that removal could be undertaken, if necessary within 1 week.

In conclusion, comparison of discontinuation rates between Norplant implants and the IUD demonstrate that, contrary to popular belief, women who have been well counseled will manifest high Norplant implants continuation rates.

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# IPPF *Medical Bulletin*

## Menstrual bleeding patterns and contraception

### Introduction

Disruption of the cyclical pattern of menstrual bleeding presents a major obstacle to the widespread continued use of many types of contraceptive. These disturbances range from amenorrhoea to heavy irregular bleeding throughout the time of administration. Irregular bleeding is the commonest reason for the discontinuation of all types of progestagen-only contraception including Pills (30–40%); injectable methods (50%); vaginal rings (30–40%) and implants (50%).[1] Similarly, excessive menstrual blood loss (MBL) is the usual cause of premature removal of the IUD.

Natural menstrual bleeding is the result of biochemical and structural changes in the endometrium induced by alterations in ovarian steroids. In the follicular phase of the cycle the high levels of oestradiol stimulate the repair and proliferation of the stroma and epithelial layers of the endometrium. During this time of unopposed oestrogen, the synthesis of receptors for oestradiol and progesterone is stimulated so that maximum concentrations are achieved around midcycle, thus making the endometrium responsive to progesterone. Following ovulation, the synthesis of steroid receptors is inhibited by progesterone. Thus, priming with oestrogen is necessary before progesterone can induce secretory changes. Normal menses occurs in response to the decline in the concentration of progesterone which happens when the corpus luteum regresses. Any alteration in the cyclical exposure of the endometrium to unopposed oestrogen, followed by oestrogen and progesterone, is likely to result in disturbances in the menstrual pattern. Drugs which have an effect on the ovarian cycle or which themselves contribute to the fluctuations in oestrogen and progesterone, as well as devices or drugs which interfere with the orderly development of the endometrium, are likely to affect the pattern of menstrual bleeding.

### Combined oral contraceptives (COCs)

Since the combined Pill inhibits ovulation and replaces the normal ovarian cycle, in the absence of erratic Pill taking, it is not likely to be associated with disturbances of menstrual bleeding. Indeed, one of the reasons why the COC is so popular is because the majority of users experience a highly predictable pattern of regular menstrual bleeding (actually withdrawal bleeding), during the Pill-free week. Nevertheless, intermenstrual bleeding is reported in some 2–20% of cycles and amenorrhoea in up to 8%. A World Health Organization Multicentre Study[2] reported, in 1982, a discontinuation rate for bleeding disturbances of 9.7% after one and 14.9% after two years of use of a combined oral contraceptive Pill containing 30 $\mu$g of ethinyl oestradiol. Abnormal bleeding is more likely with low-dose Pills and is said to improve with time. As a first approach to the management of breakthrough bleeding, a change of Pill to one containing a higher dose of oestrogen is worth trying and makes sense physiologically. The triphasic Pill was developed in an attempt to improve cycle control, but there is no good evidence to suggest that it is any better in this respect than monophasic Pills, particularly after the first three cycles.[3]

The reason why some women fail to bleed during the Pill-free week and develop amenorrhoea is not clear. It is possible that their ovaries may be totally suppressed and that in contrast to the majority of women on COCs there is no rise in the level of endogenous oestradiol during the Pill-free week. In most women on COCs the brief time unopposed oestrogen is present is likely to stimulate the development of steroid receptors which permit the endometrium to respond to oestrogen and progestagen. Women who develop amenorrhoea while on the Pill may have endometrial atrophy because of a lack of endogenous oestradiol sufficient to develop steroid receptors.

Injectable progestagen-oestrogen contraceptive methods have been developed by WHO and allow a single defined bleeding episode.[4] While these combined preparations are as effective in preventing pregnancy as injectable progestagen-only methods, the rate of discontinuation for bleeding irregularities after 12 months is low (6.3–7.5%), as is that for amenorrhoea (1.6–2.1%). Combination vaginal rings releasing a progestagen and an oestrogen have been tested by the Population Council. In a multicentre study[5] there was no difference in the incidence of intermenstrual bleeding or spotting when the ring was compared with a 30 $\mu$g combination Pill, and both methods produced similar bleeding patterns.

### Progestagen-only contraception

All methods of progestagen-only contraception are associated with a relatively high incidence of bleeding disturbances. Around 40% of women taking the progestagen-only Pill (POP) continue to ovulate regularly,[6] while the remainder will have anovulatory cycles (23%); cycles with insufficient luteal phases (21%); or amenorrhoea (15%).

When continuous exogenous progestagens are superimposed on irregularly fluctuating concentrations of endogenous steroid hormones it is hardly surprising that irregular bleeding patterns occur.[7] It is more difficult to explain the occurrence of breakthrough bleeding in the presence of high doses of progestagen (with DMPA or during the first year of Norplant use). In this case the mechanism is probably a result of endometrial factors, such as the inadequate development of steroid receptors. There is little evidence to suggest that irregular bleeding associated with POP use improves with a change to a different brand of POP if the dose of gestagen is equipotent, nor does it improve with time.[8]

In contrast, women using injectable methods tend to develop amenorrhoea with increasing duration of use (30–50% after one year and a higher percentage with long-term use). In some societies, it may be culturally unacceptable, however, to have amenorrhoea, despite the potential health benefits. Cyclical oral oestrogen administration in combination with DMPA has been

shown to be effective in producing better cycle control,[9] but converts the regimen into a much more complicated method of contraception, and may cause more side-effects and increase the risk of cardiovascular complications.

Gestagen-only subdermal implants and vaginal rings release constant amounts of steroid hormone, but are nevertheless associated with disturbances of bleeding patterns. The situation with Norplant does improve with time,[10] but in one study 26% of women abandoned the method within the first year.[11] The progestagen-only vaginal ring is associated with a similar discontinuation rate for menstrual disturbances as the POP (15%), but in studies undertaken to date, amenorrhoea appears to be an uncommon complication.[12]

### Intrauterine devices

That the use of the IUD is associated with increased MBL is undisputed. However, the mechanism underlying the phenomenon remains unclear. A local inflammatory response may cause injury to small blood vessels, alter prostaglandin synthesis and release, increase fibrinolytic activity and impair haemostasis.[13] Efforts have been concentrated on designing devices which would reduce the problem. The addition of copper to IUDs allowed a reduction in their size, while maintaining or even improving their contraceptive efficacy. Copper IUDs are associated with fewer bleeding problems than inert devices,[14] but their use still results in a higher MBL and longer duration of menstrual bleeding than occur in the natural cycle. The new flexible IUD,[15] consisting of small copper beads threaded on nylon embedded into the myometrium of the fundus, may be associated with reduced MBL, but the progestagen-releasing IUDs probably offer the best possibility of overcoming the problem. After a high incidence of bleeding/spotting days in the first three months there is a reduction in the duration and amount of bleeding in association with endometrial atrophy and, indeed, one of the commonest reasons for discontinuation in early trials was amenorrhoea.[1]

### Conclusion

It has to be remembered that the acceptance of disturbances of menstrual bleeding varies among women, depending on a number of factors including cultural considerations and the availability of alternative methods. The number of women discontinuing a method for a particular reason probably represents only a fraction of the number experiencing and tolerating that side-effect. The development of new and improved methods of contraception should not rely on a high level of tolerance of so-called 'nuisance side effects'. However, there is a real need for further research to increase our understanding of the mechanism of normal menstruation so that future contraceptive methods with a low incidence of menstrual disorders may be developed. Dr José Barzelatto, in his welcoming address to participants attending a WHO Symposium on contraception and mechanisms of endometrial bleeding held in 1988, doubted whether "it is possible at all to develop steroidal contraceptives which do not cause any bleeding irregularities" — unfortunately, he may be right.

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*(Continued at foot of next column)*

## The use of progesterone vaginal rings as contraceptives for lactating women

The contraceptive efficacy of breast feeding is high during the time of lactational amenorrhoea,[1,2] but the risk of pregnancy increases rapidly once the menstrual cycles recommence or when mothers start supplementing their infant's diet or when they are more than six months postpartum.[2,3] Lactating women who want to avoid pregnancy need to start using contraceptive methods that should not interfere with lactation and maternal or infant health. At the present time, the selection of appropriate methods for nursing women is restricted to very few alternatives because several of the methods available have a negative influence on lactation or hold potential risks for the infants.[4] For this reason, we have proposed and tested the efficacy of progesterone, the natural hormone, as a fertility regulation method during lactation.[5]

### Use of progesterone

Progesterone has no biological activity when given orally unless it is specially formulated or is given in very high doses.[6] Thus, the risk of infant exposure to progesterone is minimized in comparison with orally active compounds. To be active, the hormone must be given by a different route.

Silastic vaginal rings have proved useful for the administration of synthetic progestagens[7,8] and of progesterone.[9,10] Rings delivering 5–15 mg per day of progesterone have been tested in postpartum clinical trials to assess their contraceptive efficacy, clinical performance and influence on lactation.

The initial studies were performed in our clinic with encouraging results. The contraceptive efficacy of the progesterone vaginal ring (PVR) is similar to that of copper intrauterine devices (T-Cu) as shown in Table I. In addition, the

TABLE I. CONTRACEPTVE EFFICACY OF PROGESTERONE VAGINAL RINGS IN NURSING WOMEN

| | *Progesterone ring* | *Copper-T IUDs* | *Untreated* |
|---|---|---|---|
| Women | 484 | 531 | 236 |
| Woman-months* | 3,166 | 3,829 | 1,552 |
| Pregnancies | 2 | 3 | 50 |
| Pearl Index | 0.76 | 0.94 | 38.6 |

* Treatments were administered at day 60 ± 5 postpartum. The end of the study was at month 14 and 12 postpartum in treated and untreated women, respectively.

*(Continued from first column)*

*Owing to difficulties of space, we are unable to publish the full list of references referring to this article. However, any reader interested in receiving the list should write to the Editor of the* IPPF Medical Bulletin, *PO Box 759, Inner Circle, Regent's Park, London NW1 4LQ, UK.*

**Key reviews**

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# Progestin receptor isoforms and prostaglandin dehydrogenase in the endometrium of women using a levonorgestrel-releasing intrauterine system

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**This study has examined endometrial tissue in 14 normal women prior to insertion of a levonorgestrel-releasing intrauterine system (LNG-IUS) and thereafter longitudinally for up to 12 months post-insertion. The specific endpoints examined by immunohistochemistry were progesterone receptor (PR) subtypes A + B, oestrogen receptor (ER) and prostaglandin dehydrogenase (PGDH). Two antiprogesterone receptor antibodies, one specific to $PR_B$ subtype and the other to PR subtype A + B, were employed to examine the localization of both PR isoforms. The activity of PGDH, a progesterone dependent enzyme, was also measured. ER and $PR_{A+B}$ and PR subtype B were significantly down-regulated in glands and stroma in the presence of continuous intrauterine LNG delivery. There was an apparent increase in $PR_A$ immunoreactivity in endometrial glands between 6 and 12 months post-insertion. Consistent with down-regulation of both isoforms of PR was reduced glandular PGDH immunostaining following LNG-IUS insertion, and PGDH activity (as measured by metabolism of excess substrate *in vitro*). Furthermore, PGDH activity, known to be localized in the glands, significantly increased ($P < 0.05$) at 12 months post-insertion, coinciding with the observed increase in glandular $PR_{A+B}$ immunoreactivity at this time. Since the LNG-IUS suppresses the $PR_B$ so strongly, $PR_A$ is likely to be the subtype that mediates long term LNG action in the endometrium. $PR_B$ is the more suppressed of the two subtypes, and only $PR_A$ rises along with PGDH activity. Alterations to normal endometrial morphology and function, e.g. perturbation of normal sex steroid receptor expression, following exposure to high concentrations of local LNG, may play a role in the aetiology of bleeding disorders associated with the LNG-IUS. Further elucidation of local uterine mediators involved in the mechanism of bleeding problems is required.**

*Key words:* intrauterine levonorgestrel/PGDH/progestin receptor isoforms

## Introduction

All progestogen-only contraceptives, including the levonorgestrel-releasing intrauterine system (LNG-IUS, Mirena, Leiras Oy, Finland) are associated with the problem of break-through bleeding. Even though the LNG-IUS is an extremely effective contraceptive which dramatically reduces menstrual blood loss (Andersson and Rybo, 1990; Milson *et al.*, 1991) its use is associated with frequent and recurrent break-through bleeding in many women. Since the acceptability to women of modern approaches to fertility control, especially hormonal methods, is dependent upon the extent of menstrual bleeding disturbance associated with such methods (Odlind and Fraser, 1990), improvements in break-through bleeding rates with the LNG-IUS are highly desirable.

The actiology of menstrual aberration associated with progestogen-only contraception is not understood. In fact, there are very limited data on the local effects of levonorgestrel on endometrial physiology. Well documented fluctuations in steroid receptor concentration take place during endometrial exposure to sex steroids in the normal cycle (Sullivan *et al.*, 1988). Briefly, concentrations of glandular progesterone receptor (PR) increase in the follicular phase under the influence of oestradiol and decline following ovulation due to secretion of progesterone. There is no substantial change in endometrial stromal PR expression across the cycle (Snijders *et al.*, 1992) and in first trimester decidua (Shi *et al.*, 1993). Oestrogen receptor concentrations are also maximal in the proliferative phase and decline in both the glandular and stromal compartment in the secretory phase of the cycle (Garcia *et al.*, 1988; Snijders *et al.*, 1992). In an interesting exception, endometrium exposed to long-term systemic LNG delivered by sub-dermal implant (Norplant®) exhibits an increase in immunoreactivity of the stromal progesterone receptor when compared with control endometrium at all stages across the menstrual cycle (Critchley *et al.*, 1993).

There are two distinct subtypes of the human progesterone receptor, $PR_A$ and $PR_B$ (Clark *et al.*, 1987). $PR_A$ subtype is the shorter form, lacking 164 amino acids from the N-terminal fragment (Tung *et al.*, 1993). Our studies of progesterone receptor localization have involved two antibodies: a rabbit polyclonal against $PR_B$ isoform and a monoclonal antibody that detects both A + B subtypes. Thus we refer to $PR_{A+B}$ as the receptor detected by antibody that recognizes both subtypes of the PR and $PR_B$ as the receptor detected by antibody specific to the B-isoform. It is not possible to raise an antibody specific to the $PR_A$ isoform. We assume that $PR_A$ is the subtype responsible for positive immunoreactivity when the $PR_B$ cannot be detected. Our group has recently described the presence of $PR_B$ immunoreactivity in the nuclei of endometrial glandular and stromal cells throughout the normal menstrual cycle and in decidua of early pregnancy. PR subtype B is preferentially expressed in the mid-proliferative phase, and

declines dramatically in the secretory phase. By inference, the $PR_A$ subtype is the subtype responsible for all immunostaining during the secretory phase, premenstrually and immediately post-menstruation. Further, preferential expression of PR subtype A was observed in first trimester decidua (Wang *et al.*, 1998). It is not known whether this differential expression of the two forms of progesterone receptor in endometrium results in different responses to steroid exposure. There are no data on progesterone receptor subtype expression in levonorgestrel-exposed endometrium.

The local release of vasoactive substances such as prostaglandins has been implicated in the contraceptive actions of intrauterine contraceptive devices. The presence of an intrauterine device (IUD) increases the production of prostaglandin $E_2$ ($PGE_2$) in secretory endometrium (Hillier and Kasonde, 1976). In studies of decidua exposed to antigestogens, blockade of the action of progesterone results in a decrease in prostaglandin metabolism and an increase in prostaglandin E, which in turn may facilitate leukocyte traffic in the endometrium. The interaction between progesterone, prostaglandins and leukocyte traffic are of relevance to the contraceptive effects of the IUD. The main prostaglandin metabolizing enzyme, prostaglandin dehydrogenase (PGDH), has been shown to be progesterone dependent (Casey *et al.*, 1980).

This study has therefore examined endometrial tissue in normal women prior to insertion of a levonorgestrel-releasing intrauterine system (LNG-IUS) and thereafter longitudinally for up to 12 months post-insertion in order to ascertain changes in endometrial sex steroid receptor localization and activity of PGDH, a progesterone dependent enzyme, during local delivery of levonorgestrel to the uterine cavity.

## Materials and methods

Ethical approval for the study was obtained from Lothian Research Ethics Committee (reference: 1702/94/6/44). Informed consent was obtained from 14 women aged between 32 and 48 years (median age 37 years). All subjects were fertile, had reported regular menstrual cycles (cycle length 25–35 days) and had not used hormonal or intrauterine contraception in the 6 months prior to inclusion in the study. The indication for insertion of the LNG-IUS was either for contraception ($n$ = 10) or heavy menstruation ($n$ = 4). The study was longitudinal, with each subject acting as her own control. All subjects underwent a pre-insertion endometrial biopsy either in the proliferative ($n$ = 7) or secretory ($n$ = 7) phase of the cycle, immediately after which the LNG-IUS was inserted. The stage of the cycle prior to insertion of the LNG-IUS was defined with reference to serum sex steroid concentrations and histological dating, according to the criteria of Noyes *et al.* (1950). Biopsies were performed in an outpatient setting with a Pipelle suction curette (Laboratoire CCD, Paris, France). Further endometrial samples were collected 1, 3, 6 and 12 months following insertion of the LNG-IUS. Since histological appearances were indistinguishable in the follicular or luteal phase, once the LNG-IUS was *in situ*, data at each time period (i.e. 1, 3, 6 or 12 months) post-IUS insertion were pooled regardless of cycle stage. All endometrial tissue samples were fixed overnight in 10% neutral buffered formalin at 4°C, rinsed and stored in 70% ethanol and thereafter routinely wax embedded. Sections 5 µm thick were cut for routine histopathology (haematoxylin and eosin staining) and immunohistochemistry (progesterone receptor, subtypes A + B, progesterone receptor subtype B, oestrogen receptor and PGDH immunolocalization). Tissue was also transported to the laboratory in ice-cold RPMI 16/40 medium for measurement of PGDH activity in the endometrial cytosol. A venous blood sample was collected at the time of biopsy. Serum was separated and frozen at –20°C for subsequent radioimmunoassay of oestradiol and progesterone (Yong *et al.*, 1992). The inter-assay coefficients of variation (CV) for these assays were 11.0 and 10.0% respectively; intra-assay CV were 8.0 and 8.0% respectively.

### *In-vitro measurement of PGDH activity*

Tissue was washed in ice-cold saline, weighed, chopped with scissors and homogenized for 20 s in 0.5 ml of ice cold metabolism buffer [20% glycerol, 2 mM dithiothreitol (Sigma, Dorset, UK) in 0.1 M phosphate buffer, pH 8.4]. Homogenate was centrifuged at 2000 *g* in a refrigerated centrifuge at 4°C and supernatant was stored at –40°C until assayed. PGDH activity in all samples was determined at the same time.

Frozen supernatant was thawed on ice and diluted in metabolism buffer. Samples of 100 µl of enzyme were incubated in 1 ml metabolism buffer containing 1 mM NAD (Sigma) and 5 µg $PGE_2$. After 30 min, the reaction was stopped by adding 2 ml of methoxyamine hydrochloride (10 mg/ml) in acetate buffer pH 5 to derivatize keto groups to their methyl oxime form. 15-Keto PGE was measured as its methyl oxime by ELISA, using a specific antibody and 15-keto PGE conjugated to horse radish peroxidase.

### *Immunohistochemistry procedures*

All immunohistochemical protocols were optimized to determine the correct conditions for maximal specific staining, and all negative controls displayed absent immunostaining.

### *Progesterone receptor (subtypes A + B) immunoreactivity with NCL-PGR antibody*

Tissue sections were dewaxed and rehydrated in descending grades of alcohol to water. Tissue sections were washed in distilled water and 0.1 M Tris buffered saline (TBS, pH 7.4–7.6, for 10 min). Non-specific endogenous peroxidase activity was blocked with 3% hydrogen peroxide in distilled water for 5–10 min at room temperature. An antigen retrieval step was performed. Tissue sections were microwaved at high power in 0.01 M sodium citrate buffer (pH 6.0) for 10 min and then allowed to stand in the microwave oven for a further 20 min. After a further wash in buffer, tissue sections were exposed to a 20 min non-immune block using diluted normal horse serum. The primary antibody raised in mouse against human progesterone receptor was used at a dilution of 1:40 (NCL-PGR, recognizing A + B subtypes, Novocastra Laboratories, Newcastle, UK). Following primary antibody binding, the sections were incubated for 30 min at room temperature with biotinylated horse anti-mouse IgG (Vecta stain, PK-4002; Vector Laboratories, Peterborough, UK). Sections were thereafter incubated for 30 min at room temperature with a mixture of avidin and biotin complex coupled to a horseradish peroxidase enzyme (Vecta stain elite, PK 6101; Vector Laboratories). The site of bound enzyme was identified by application of 3,3-diaminobenzidine in $H_2O_2$ (DAB Kit, SK-4100; Vector Laboratories). Thereafter tissue sections were washed in distilled water and counterstained with Harris' haematoxylin, a non-specific nuclear stain. Sections were rinsed with tap water, dehydrated and cleared in xylene before mounting in Pertex (Cellpath, Hemel Hempstead, UK). Negative controls were included by replacing the primary antibody with mouse immunoglobulin (at a matching concentration) at a dilution of 1:6000 in PBS.

Similar protocols were used for localization of progesterone receptor

subtype B ($PR_B$), oestrogen receptor (ER) and PGDH. Specific features in each immunostaining protocol were as follows.

***Progesterone receptor subtype B ($PR_B$) immunohistochemistry***

No antigen retrieval step was required to expose the epitope. A non-immune block was conducted with normal goat serum. Tissue sections were incubated with a 1:200 dilution of anti progesterone receptor B antibody (rabbit anti-human polyclonal antibody, raised against a 19 amino acid sequence from the N-terminal end, unique to $PR_B$ subtype –DQQSLSDVEGAYSRAEATR– and coupled through a C-terminal cysteine to keyhole limpet haemocyanin) in TBS for 60 min at 37°C. Western blotting of endometrial tissue samples collected during the periovulatory phase revealed a strong band at expected molecular mass of 120 kDa (Wang *et al.*, 1998). Primary antibody binding was detected with an avidin–biotin peroxidase detection system. Sections were incubated with a biotinylated goat anti-rabbit IgG antibody made up in dilute normal goat serum for 60 min at room temperature. Thereafter the protocol was as described above for localization of the progesterone receptor. Negative controls were performed by replacing the primary antibody with non-immune serum of the equivalent concentration.

***Oestrogen receptor (ER) immunohistochemistry***

Pretreatment of the sections was necessary for localization of the oestrogen receptor. Tissue sections were microwaved at high power in 0.01 M sodium citrate buffer (pH 6.0) for 10 min then allowed to rest in the microwave for 20 min. The protocol was thereafter conducted as described above for the progesterone receptor. Primary antibody ER1D5 (DAKO Laboratories, High Wycombe, UK) was used at a dilution of 1:25. Negative controls were included by replacing primary antibody by non-immune mouse immunoglobulin at the equivalent concentrations.

***Prostaglandin dehydrogenase (PGDH) immunohistochemistry***

Detection of PGDH immunoreactivity employed a rabbit polyclonal antibody (Cascade Biochem Ltd, Reading, UK) with an avidin–biotin peroxidase detection system. Endogenous peroxidase activity was quenched with 3% hydrogen peroxide in distilled water for 10 min at room temperature. A non-immune block was conducted using 10% normal swine serum for 20 min at room temperature. Sections were incubated overnight with the primary antibody (dilution 1:500) at 4°C. Biotinylated secondary antibody (biotinylated swine anti-rabbit) and ABC complex (Vecta stain, ABC Kit, PK 4002; Vector Laboratories) were then applied for 30 min each at room temperature. The peroxidase substrate diaminobenzidine (DAB) was used to visualize the reaction (SK4100; Vector Laboratories). Slides were lightly counter stained with Harris haematoxylin. Rabbit immunoglobulin at a dilution of 1:500, i.e. the equivalent concentration as primary antibody, was substituted for negative control sections.

*Scoring and immunohistochemistry analysis*

A semi-quantitative scoring system was employed for assessment of intensity and localization of immunoreactivity in entire tissue sections. The score of zero indicated an absence of immunoreactivity; 1 = faint immunoreactivity; 2 = strong immunoreactivity and 3 = very intense immunoreactivity. We have previously reported in endometrial tissue sections a high correlation (0.963) of objectively measured immunoreactivity (measured by computerized image analysis) and subjective semi-quantitative scoring of immunostaining patterns. Such data supports the subsequent statistical analyses performed on the semi-quantitative scores of sex steroid receptor immunoreactivity (Wang *et al.*, 1998).

A one-way analysis of variance (ANOVA) with Fisher's PLSD coefficient was used to evaluate whether or not there were significant differences in the expression of epitopes. The results with a $P$ value of $\leq 0.05$ or $\leq 0.01$ were considered significant differences.

**Table I.** Serum oestradiol (pmol/l) and progesterone (nmol/l) concentrations at time of endometrial biopsy, prior to and following insertion of a LNG-IUS

| Biopsy time | | *n* | Serum oestradiol range mean (SE) | Serum progesterone range mean (SE) |
|---|---|---|---|---|
| Pre-insertion: proliferative phase | | 5* | 62–343<br>145 (53) | 0–10<br>3.4 (1.9) |
| Pre-insertion: secretory phase | | 7 | 166–614<br>300 (52.7) | 6–28.6<br>17.7 (2.9) |
| Post-insertion | 1 month | 11 | 217–2281<br>637 (201) | 0–23.2<br>3.7 (1.1) |
| | 3 months | 13 | 49–813<br>380.7 (105.8) | 0–19.9<br>3.8 (1.1) |
| | 6 months | 14 | 69–1929<br>446.2 (120.6) | 0–16.3<br>3.7 (1.0) |
| | 12 months | 14 | 67–1288<br>460.4 (124.4) | 0–56.6<br>11.6 (3.1) |

*Serum oestradiol and progesterone concentrations were unavailable from two patients whose biopsies prior to IUS insertion were collected in the proliferative phase (hence $n = 5$).

## Results

Prior to insertion of the LNG-IUS, endometrial biopsies conducted in the follicular and luteal phases of the ovarian cycle displayed normal proliferative and secretory features respectively. All subjects in whom biopsies were performed in the follicular phase (proliferative histology) had circulating progesterone concentrations of ≤10 nmol/l (range 0–10, mean 3.4, SEM 1.9). Women in whom biopsies were performed in the luteal phase (secretory histology) had serum progesterone concentrations ranging between 6 and 28.6 nmol/l (mean 17.7, SEM 2.9) (see Table I).

Insertion of a LNG-IUS produced widespread morphological changes in endometrial histology: a pseudo-decidualized stroma with atrophic glands was observed in all biopsies collected following insertion of the LNG-IUS.

***$PR_{A+B}$ immunoreactivity***

Prior to LNG-IUS insertion, all proliferative phase biopsies displayed positive $PR_{A+B}$ immunoreactivity in both glands and stroma. Secretory phase endometrial biopsies collected prior to IUS insertion showed reduced $PR_{A+B}$ immunostaining in glands ($P \leq 0.001$) but no reduction in stromal $PR_{A+B}$ immunoreactivity. However, a significant decrease in $PR_{A+B}$ immunoreactivity was observed in the stromal and glandular compartments of endometrium (see Figure 1a–c) following insertion of a LNG-IUS. Figure 2 illustrates the change in glandular and stromal $PR_{A+B}$ immunoreactivity in endometrium following insertion of a levonorgestrel IUS.

There were significantly lower ($P \leq 0.001$) $PR_{A+B}$ immunostaining levels in the glandular epithelium 1, 3 and 6 months after insertion of a LNG-IUS compared to progesterone receptor immunoreactivity in biopsies prior to insertion of the

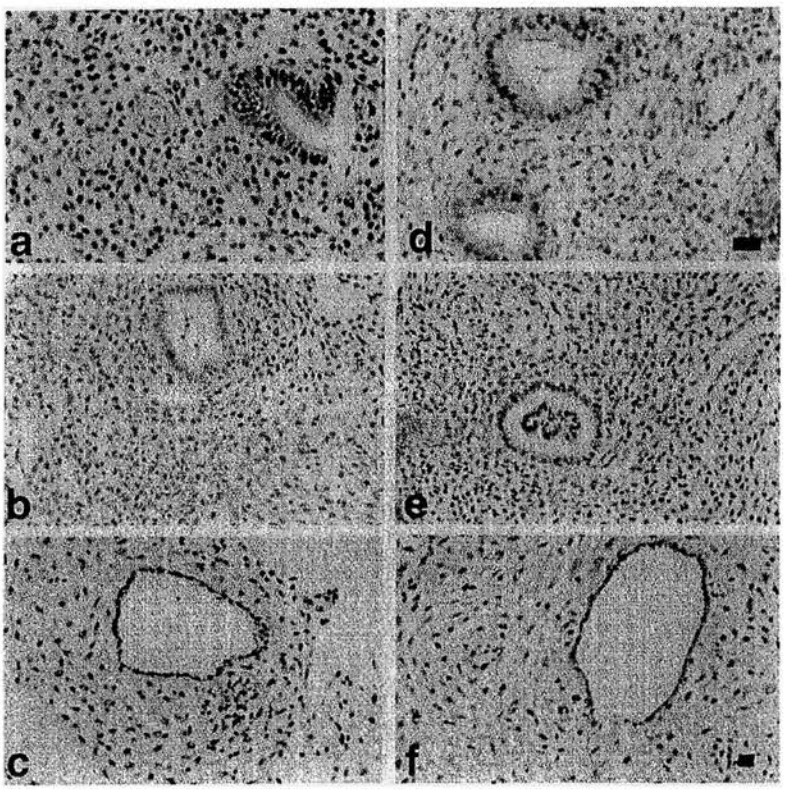


**Figure 1.** Progesterone receptor ($PR_A$ + $PR_B$) and progesterone receptor subtype B stromal and glandular immunoreactivity in endometrium exposed to intrauterine LNG. (**a**) Strong positive PR (A + B) immunostaining in proliferative endometrium prior to insertion of a LNG-IUS. (**b**) Reduced endometrial PR (A + B) immunostaining 1 month post-insertion of a LNG-IUS. (**c**) PR (A + B) immunostaining 12 months post-LNG-IUS insertion. Note increased immunostaining in glands and stroma. (**d**) Strong positive $PR_B$ immunoreactivity in proliferative endometrium prior to LNG-IUS insertion. (**e**) Low intensity $PR_B$ immunostaining 1 month post-insertion of a LNG-IUS. (**f**) Persistent low $PR_B$ immunoreactivity 6 months following insertion of a LNG-IUS. Scale bar for **a**, **b**, **d**, **e** (shown in **d**) = 50 μm. Scale bar for **c** and **f** (shown in **f**) = 25 μm.

intrauterine system collected in the proliferative phase. These levels were equivalent to those seen in the luteal phase. However, between 6 and 12 months following insertion, there was an increase in $PR_{A+B}$ immunostaining in endometrial glands ($P < 0.05$). In the endometrial stroma, $PR_{A\,|\,B}$ immunostaining was also significantly decreased 1, 3, and 6 months following insertion of the LNG-IUS when compared to pre-insertion stromal immunoreactivity ($P < 0.05$), but, unlike the glands, there was no increased staining evident in the 12 month samples.

### *$PR_B$ immunoreactivity*

PR subtype B immunostaining was evident in glands and stroma in proliferative phase biopsies prior to IUS insertion, although immunostaining was much less intense than when an antibody recognizing A + B subtypes was employed. Glandular PR subtype B immunoreactivity was significantly reduced in the secretory phase ($P < 0.01$) but persisted in the stromal compartment of secretory phase biopsies collected pre-IUS insertion. Figure 1d–f and Figure 3 illustrate a decrease or absence of progesterone receptor subtype B immunoreactivity in both glandular and stromal ($P < 0.01$) compartments of endometrium 1, 3, 6 and 12 months following insertion of a LNG-IUS, with no indication of an increase in immunostaining in the 12 month samples.

### *Oestrogen receptor (ER) immunoreactivity*

ER immunoreactivity was also confined to the nuclei of endometrial glands and stromal tissue. Positive strong immunostaining was displayed in glands and stroma of proliferative phase biopsies prior to LNG-IUS insertion. Pre-insertion biopsies collected in the secretory phase displayed reduced glandular ($P < 0.05$) and stromal immunoreactivity (not significant). There was a significant fall ($P < 0.001$) in oestrogen receptor

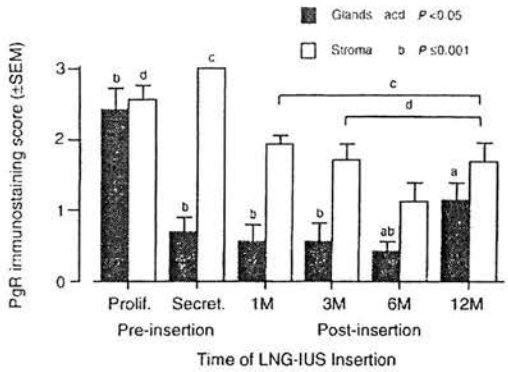


**Figure 2.** Mean $PR_{A+B}$ immunostaining scores (± SEM) in endometrium prior to and after insertion of a LNG-IUS. Prolif. = proliferative; Secret. = secretory; M = months.

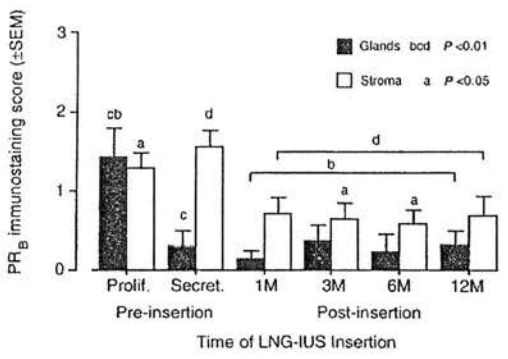


**Figure 3.** Mean $PR_B$ immunostaining scores (± SEM) prior to and following insertion of a LNG-IUS. Prolif. = proliferative; Secret. = secretory; M = months.

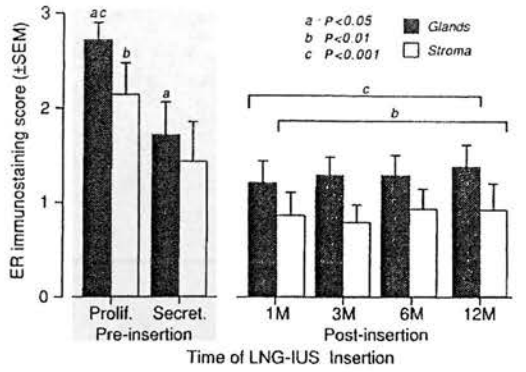


**Figure 4.** Mean oestrogen receptor (ER) immunostaining scores (± SEM) prior to and after LNG-IUS insertion. Prolif. = proliferative; Secret. = secretory; M = months.

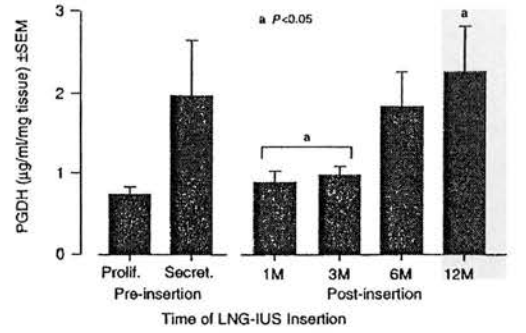


**Figure 5.** In-vitro prostaglandin dehydrogenase (PGDH) activity (µg/ml per mg tissue) ± SEM. Pre-insertion biopsies ($n$ = 8: proliferative $n$ = 3, secretory $n$ = 5); Post-insertion biopsies (at 1 month $n$ = 8; 3 months $n$ = 12; 6 months $n$ = 11; 12 months $n$ = 7).

immunoreactivity in the glandular compartment of endometrial biopsies collected at 1, 3, 6 and 12 months post-insertion, when compared with endometrial tissue collected pre-insertion in the proliferative phase (Figure 4). Oestrogen receptor immunoreactivity in stromal endometrial tissue was significantly reduced ($P < 0.01$) 1, 3, 6 and 12 months following insertion of the IUS when compared with stromal endometrium collected from subjects prior to insertion in the proliferative phase (Figure 4). These levels were equivalent to those seen in the luteal phase, and showed no increase in the 12 month samples.

### *PGDH metabolism*

PGDH activity, as measured by metabolite (µg/ml per mg tissue) was greater in endometrial samples collected in the secretory phase. Low levels of PGDH activity were observed following insertion of a LNG-IUS both 1 and 3 months post-insertion. Metabolism significantly increased ($P < 0.05$) at 12 months post-IUS insertion (Figure 5).

Positive immunoreactivity for PGDH was observed in the glandular cytoplasm from all endometrial biopsies collected prior to insertion of the LNG-IUS during the secretory phase of the cycle. Reduced PGDH immunostaining was observed in endometrial tissue collected following insertion of the LNG-IUS (data not shown).

### *Serum oestradiol and progesterone concentrations*

Circulating serum oestradiol and progesterone concentrations at the time of endometrial biopsy are documented in Table I.

## Discussion

This study describes a significant decline in immunostaining of ER and PR (subtype A + B) in glands and stroma in endometrium exposed to intrauterine levonorgestrel. Furthermore, the availability of an antibody directed against a sequence at the N terminal end, unique to $PR_B$ subtype, has demonstrated a more substantial and sustained down-regulation of the

$PR_B$ subtype in the glands and stroma of the LNG-exposed endometrium, whereas a distinct increase in staining with the $PR_{A+B}$ antibody was evident in the glands at 12 months. Consequently, the data herein show by inference that the $PR_A$ subtype is likely to be the isoform mediating LNG action in the endometrium.

The observation of down-regulation of $PR_B$ (see Figure 3) in endometrium exposed to intrauterine levonorgestrel is consistent with our own observations of progesterone receptor subtype expression in the normal cycle and in early decidua (Wang *et al.*, 1998). It would appear that regardless of whether the exposure of the endometrium to high concentrations of progestin was endogenous (as in luteal phase or early pregnancy) or exogenous (LNG-IUS) $PR_B$ is suppressed to a greater extent than the $PR_A$ subtype.

We previously reported that $PR_A$ is the predominant subtype in secretory endometrium and decidua of early pregnancy, that is, in a progesterone dominated steroid environment (Wang *et al.*, 1998). $PR_A$ protein is also the dominant isoform, as determined by Western blot analysis in human myometrium (Viville *et al.*, 1997). The significance of the predominance of $PR_A$ is not known. Morphologically, the endometrium in the presence of a LNG-IUS shows features of decidualized stroma (Nilsson *et al.*, 1978; Silverberg *et al.*, 1986). Hence in the presence of 'pseudo-decidualization', the predominance of $PR_A$ is consistent with observations of PR subtype expression in early decidua (Wang *et al.*, 1998). Differential expression of PR subtypes is likely to determine response to progestins, although the action of ligand occupied $PR_B$ receptors may work through an alternative mechanism (Tung *et al.*, 1993). In endometrium exposed to a local exogenous LNG (LNG-IUS), sufficient $PR_A$ isoform is maintained to mediate the long term morphological and functional characteristics of progestin action, for example decidualization.

There was an interesting apparent increase in $PR_A$ immunoreactivity in endometrial glands between 6 and 12 months post-insertion. Further, this apparent rise in $PR_A$ was related to increased PGDH activity between 6 and 12 months following insertion of the intrauterine system. However, there was an apparent discrepancy between PGDH activity (Figure 5) and PR concentration (Figure 2) during the secretory phase. This may have been due to the chronic high exposure of the endometrium to local progestins. Nevertheless, the observations described here concerning prostaglandin metabolism (reduced PGDH immunostaining and reduced in-vitro PGDH activity post-LNG-IUS insertion) support the hypothesis that with a down-regulation of PR, the endometrium is less responsive to progestin-mediated events.

The observations of elevated PGDH immunoreactivity in endometrial biopsies collected in the secretory phase prior to insertion of a LNG-IUS are consistent with reported data concerning PGDH enzyme activity in the secretory phase and premenstrually (Casey *et al.*, 1980). The decline in PGDH immunostaining following insertion of a LNG-IUS is consistent with our observation of reduced $PR_{A+B}$ and $PR_B$ immunoreactivity post-insertion of a LNG-IUS. From a functional viewpoint, if reduced steroid receptor is available to bind the ligand then only a limited functional response can be initiated (that is, reduced induction of PGDH activity). This study has thus demonstrated a consistent functional response of the endometrium to the reduced number of progesterone receptors. The continued suppression of $PR_B$ by exogenous LNG is by inference, at least in part, mediated by the $PR_A$ subtype.

The in-vitro data for PGDH activity are in keeping with these observations. Prostaglandin metabolism is elevated in tissue collected in the secretory phase, prior to insertion of a LNG-IUS and reduced thereafter. Small sample numbers ($n = 3$) precluded estimation of a significant difference when compared with secretory phase biopsies. The observation is, however, entirely consistent with the literature (Casey *et al.*, 1980). Following insertion of the LNG-IUS, metabolism was low at 1 month and 3 months. This is consistent with the down-regulation of PR in the glands of LNG-exposed endometrium. However, there was a significant increase in metabolism (PGDH activity) 12 months post-LNG-IUS insertion. This coincided with the observed significant increase in glandular PR immunoreactivity (which by inference was presumably $PR_A$ subtype) 12 months following insertion of the LNG-IUS.

In the present study, a significant reduction in ER immunoreactivity has been reported up to 12 months following insertion of the LNG-IUS. In the normal cycle there is a significant decline in the ER of the glands and stroma in the functional layer of endometrium, with the transition from proliferative to secretory phase of the cycle. However, there is no significant fall in ER (or PR) immunoreactivity in the stromal compartment of the basal endometrium (Snijders *et al.*, 1992). The endometrium of users of a LNG-IUS is atrophic, but is morphologically distinct from normal basal endometrium (own observations). At any time, the steroid environment within the endometrium will reflect the local progestogen (LNG) levels and the circulating serum oestradiol and progesterone concentrations. Mean serum oestradiol concentrations remained in the mid follicular range (Critchley *et al.*, 1990) during the 12 months following LNG-IUS insertion. Mean serum progesterone levels were indicative of the fact that biopsies were collected during either the follicular or luteal phases (see Table I).

Short-term administration of synthetic progestogens decreases the PR content of both endometrial epithelium and stroma in pre- and post-menopausal women (Lane *et al.*, 1988). Continuous delivery of levonorgestrel exerts part of its contraceptive action via PR in endometrium and thus subsequent biological activity is presumed to be dependent upon the concentrations and availability of functional PR (Lau *et al.*, 1996). The observations reported here on PR expression in endometrium exposed to intrauterine levonorgestrel are completely opposite to observations in endometrium from Norplant® users (sub-dermal LNG). In the presence of elevated circulating progestogen concentrations, PR immunoreactivity was persistently raised in Norplant® exposed endometrium. The mechanism by which this observation may be explained and whether the observed increase in stromal PR immunoreactivity is associated with an increased number and concentration of functional PR is unknown (Critchley *et al.*, 1993). According to Lau *et al.*

(1996), Norplant results in a decrease in PR mRNA levels as measured by in-situ hybridization, which implied a change in turnover rate of PR mRNA and protein. Similar data on PR mRNA levels in endometrium exposed to intrauterine delivery of levonorgestrel are not yet available.

Pekonen *et al.* (1992) have also observed functional differences between continuous local intrauterine and subdermal levonorgestrel delivery. Intrauterine LNG was a potent stimulator of stromal cell IGFBP-1 production. IGFBP-1 is a product of decidualized stromal cells (Bell, 1991). Subdermal delivery of LNG produced no such effect. This observed difference is likely to reflect dose-dependency effects of LNG. Intrauterine LNG produced endometrial LNG levels 1000 times greater than serum concentrations. The latter are of the same order of magnitude with subdermal implants (Nilsson *et al.*, 1982; Pekonen *et al.*, 1992). In the presence of such high local progestin concentrations, endogenous, systemic progesterone would be masked, despite circulating progesterone concentrations remaining in the normal follicular–luteal phase range (Table I). Women using a LNG-IUS usually have normal ovulatory cycles (Luukkainen, 1991) and there is no reduction in oestradiol concentrations (Luukkainen *et al.*, 1990). LNG, however, is not progesterone and the ligand (LNG)–receptor complexes may not necessarily reproduce all the classic 'progesterone' actions.

Insertion of a LNG-IUS produced widespread morphological changes in endometrial histology. In this study, a pseudo-decidualized stroma, with atrophic glands, was evident in all biopsies collected post-insertion of the IUS. These observations are consistent with earlier reports (Nilsson *et al.*, 1978; Silverberg *et al.*, 1986). A more detailed description of the histological features in biopsies in this series will be reported elsewhere.

The dramatic reduction in menstrual blood loss (Andersson and Rybo, 1990; Milson *et al.*, 1991) described in users of a LNG-IUS has been considered to be due to epithelial and glandular endometrial atrophy (Nilsson *et al.*, 1978; Silverberg *et al.*, 1986) associated with the LNG-IUS. However, disturbances in endometrial bleeding associated with the intrauterine system remain a major problem for users. It is likely that subtle endometrial mechanisms responsible for the control of normal uterine bleeding have been disturbed. The present data provide novel information on the perturbation of local sex steroid receptor expression (down-regulation) in the presence of a LNG-IUS and evidence to support interference with normal function (PGDH activity). Thus disturbance of sex steroid receptor expression, as described in this study, may play a role in the control of mechanisms responsible for aberrations in normal bleeding patterns. Interestingly, bleeding patterns are reported to improve (Luukkainen, 1991) 6 months or so following insertion of a LNG-IUS, at a time when at least PR (by inference subtype A) had somewhat increased. Further work is necessary to elucidate the mechanisms responsible for this major problem of menstrual aberration with progestin-only contraceptive methods. Examination of more local mechanisms in endometrium exposed to an intrauterine levonorgestrel system should help explain some of the potential mechanisms regulating endometrial bleeding.

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# Morphological and functional features of endometrial decidualization following long-term intrauterine levonorgestrel delivery

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**Irregular bleeding remains a common reason for the discontinuation of progestin-only contraception. The levonorgestrel releasing intrauterine system (LNG–IUS) has profound morphological effects upon the endometrium. Specific features are gland atrophy and extensive decidual transformation of the stroma. Morphological changes in the endometrium may be associated with perturbation of mechanisms regulating normal endometrial function. This study describes endometrial stromal and glandular features prior to and up to 12 months following insertion of the LNG–IUS. Comparison is made with first trimester decidua. In order to elucidate further mechanisms governing endometrial function with local intrauterine delivery of LNG, we here report histological features consistent with decidualization; a significant increase in granulocyte-macrophage colony stimulating factor (GM–CSF) immunoreactivity in decidualized stromal cells; glandular and stromal prolactin receptor expression and an infiltrate of CD56+ large granular lymphocytes and CD68+ macrophages. We are unaware of previous reports which have documented longitudinally both morphological and functional observations in endometrium exposed to local intrauterine levonorgestrel delivery. These studies demonstrate that long-term administration of intrauterine levonorgestrel results in features of altered morphology and function. No correlation was apparent between the end points in the study and the bleeding patterns described by the subjects. Further evaluation of these features in the context of menstrual bleeding experience may contribute to a better understanding of this troublesome side-effect which often leads to dissatisfaction and discontinuation of the intrauterine system.**

*Key words:* decidualization/GM–CSF/intrauterine levonorgestrel/leukocytes/prolactin receptor

## Introduction

Irregular bleeding remains the single most common indication for discontinuation of progesterone-only methods of contraception (Findlay, 1996) and the aetiology of this frequent complaint is not understood. Few data exist concerning endometrial stromal changes in users of progestin-only contraception. Indeed attention has been drawn to the fact that the 'short phase of decidualization' observed following commencement of progesterone-only contraception may be transient and thus the cells are not 'true decidual cells' with the consequence that factors not normally associated with decidual cells may be produced (Findlay, 1996).

Steroid releasing intrauterine devices have profound morphological effects on the endometrium. Specific features are suppression of proliferative activity and atrophy with extensive decidual transformation of the stroma (Silverberg *et al.*, 1986; Sheppard, 1987). Intrauterine devices elicit characteristic local changes in leukocyte populations within the endometrium, including infiltration of macrophages, lymphocytes and neutrophils which appear in the stroma and epithelium (Sheppard, 1987). Mechanisms concerned with leukocyte distribution in the endometrium of IUD users are not known. During the normal menstrual cycle there is a late secretory phase increase in stromal leukocytes (Bulmer *et al.*, 1988) with a pre-menstrual increase in stromal macrophages (Kamat and Isaacson, 1987). Both the late secretory phase endometrium and early decidua contain a significant population of leukocytes, the majority of which are CD56+ large granular lymphocytes (LGL) (King and Loke, 1991).

The temporal expression of prolactin in the uterus implicates a role for this hormone in decidualization and hence implantation (Wu *et al.*, 1995). Prolactin is an immunoregulating agent and may play a role in leukocyte function. Our group (Jones *et al.*, 1998) has recently reported the localization of the prolactin receptor protein in glandular epithelium and some stromal cells from the mid to late secretory phase of the menstrual cycle and in first trimester decidua, coinciding with the onset of decidualization.

Few data are available concerning endometrial cytokines and their role in mechanisms concerned with endometrial bleeding. Granulocyte-macrophage colony stimulating factor (GM–CSF) is an activating growth factor for granulocytic and monocytic cells. Human GM–CSF is considered to be steroid-regulated (Sharpe-Timms *et al.*, 1994). GM–CSF is synthesized by epithelial cells in the murine pregnant and non-pregnant uterus (Robertson *et al.*, 1992) and is likely to be regulated in the mouse primarily by oestrogen. In the human, epithelial cells are the major contributor to production (Giacomini *et al.*, 1995) and variations are reported in the level of immunohistochemical expression of GM–CSF in endometrial epithelial cells (Sharpe-Timms *et al.*, 1994). Furthermore, GM–CSF production by resident leukocytes (macrophage and

large granular lymphocytes) has been demonstrated (Jokhi *et al.*, 1994). A potential role for endometrial GM–CSF in macrophage recruitment into the stroma has been reported in rodents (Robertson and Seamark, 1992).

This study describes endometrial stromal and glandular features prior to and up to 12 months following insertion of a levonorgestrel-releasing intrauterine system (LNG–IUS; Mirena, Leiras Oy, Finland). The LNG–IUS has an inert frame on which a silastic capsule has been attached to the vertical arm, releasing 20 μg levonorgestrel every 24 h to the uterine cavity from a total load of 52 mg LNG (Luukkainen *et al.*, 1990). A comparison has been made with the morphological features of first trimester decidua.

## Materials and methods

Ethical approval for the study was obtained from Lothian Research Ethics Committee (reference: 1702/94/6/44). Informed consent was obtained from 14 women aged between 32 and 48 years (median age is 37 years). All subjects were fertile, described regular menstrual cycles (cycle length 25–35 days) and were not using hormonal or intrauterine contraception in the 6 months prior to inclusion in the study. The indication for insertion of the LNG–IUS was either for contraception ($n$ = 10) or heavy menstruation ($n$ = 4). The study was longitudinal with each subject acting as her own control. All subjects underwent a pre-insertion endometrial biopsy either in the proliferative ($n$ = 7) or secretory ($n$ = 7) phase of the cycle. The stage of the cycle prior to LNG–IUS insertion was defined according to the criteria of Noyes *et al.* (1950). Biopsies were performed in an outpatient setting with a pipelle suction curette (Laboratoire CCD, Paris, France). Further endometrial samples were collected 1, 3, 6 and 12 months following insertion of the LNG–IUS. Once the LNG–IUS was *in situ*, the histological appearance of endometrium samples was indistinguishable whether collected in the follicular or luteal phase, hence data at time period of 1, 3, 6 and 12 months were pooled.

In addition decidual tissue was collected from ten women (8–10 weeks amenorrhoea) undergoing surgical termination of pregnancy. Decidual biopsies were stained with a monoclonal antibody against cytokeratin to confirm absence of trophoblast tissue (decidua parietalis). All endometrial and decidual tissue samples were fixed overnight in 10% neutral buffered formalin at 4°C, rinsed and stored in 70% ethanol and thereafter routinely wax embedded. Sections 5 μm thick were cut for routine histopathology (haematoxylin and eosin staining) and immunohistochemical localization of granulocyte macrophage colony stimulating factor (GM–CSF), prolactin receptor, CD56+ large granular lymphocyte (LGL), macrophage (CD68) and neutrophil elastase immunoreactivity. Our laboratory has recently described the localization of progesterone receptors (subtypes A + B) and oestrogen receptors in normal endometrium and decidua (Wang *et al.*, 1998) and in endometrium exposed to intrauterine LNG (Critchley *et al.*, 1998).

### *Immunohistochemistry procedures*

#### *Prolactin receptor immunolocalization*

Paraffin sections were dewaxed and rehydrated through descending grades of ethanol to distilled water. The sections were then washed twice in 0.1 M phosphate buffered saline (PBS) for 5 min. Endogenous peroxidase activity was quenched by immersion in 3% hydrogen peroxide ($H_2O_2$, BDH Laboratory Supplies, Poole, UK) in distilled water for 5 min and then sections were again washed. Non-specific binding was reduced by a 20 min incubation with non-immune goat serum (Vector Stain Elite®; Vector Laboratories, Peterborough, UK) in a humidified chamber at room temperature, following which the excess was carefully removed and the primary antibody (Nevalainen *et al.*, 1996) (rabbit polyclonal raised against a rat peptide sequence common to the short and long form of the receptor, kindly supplied by Dr P. Ingleton, University of Sheffield) was applied at a dilution of 1:50. Slides were incubated overnight (17 ± 1 h) at 4°C. Antibody binding was detected by the sequential application of biotinylated goat anti-rabbit IgG and an avidin–biotin–peroxidase complex (ABC Vector Stain®; Vector Laboratories).

The substrate 3.3′ diaminobenzidine (DAB, Vector Laboratories) was then utilized to visualize positive immunoreactivity. Finally, sections were counter-stained with Harris' haematoxylin (Pioneer Research Chemicals Ltd, Colchester, UK), dehydrated and cleared in xylene before mounting in Pertex® (Cellpath, Hemel Hempstead, UK).

Positive controls included for the prolactin receptor immunohistochemistry were sheep pituitary sections (Tortonese *et al.*, 1996) and human term fetal membranes (Maaskant *et al.*, 1996). Negative controls had an equivalent concentration of non-immune rabbit immunoglobulin substituted for the primary antibody to exclude the possibility of non-specific binding.

### *Granulocyte macrophage colony stimulating factor (GM–CSF)*

#### *Immunolocalization*

A similar protocol as above was used for the localization of GM–CSF. The primary antibody was raised in the mouse against human GM–CSF [GM–CSF (ZM-213), Genzyme Diagnostics, Kent, UK]. Incubation with the primary monoclonal antibody at a dilution of 1:75 took place for 90 min at 37°C. Thereafter the protocol was similar to that employed for prolactin receptor. Tris buffered saline (TBS) was used throughout instead of PBS. The second antibody was a horse anti-mouse antibody (Vector Laboratories) and the avidin–biotin–peroxidase complex ABC Elite® (Vector Laboratories). Negative controls were performed by replacing the primary antibody with mouse immunoglobulin at the same dilution (1:75).

The positive controls were a GM–CSF expressing cell line (MG-63 cells, derived from a male osteosarcoma cell line and gift of Dr Fouad Habib, Western General Hospital, Edinburgh). MG-63 cells were grown up on Chamber slides (Nunc Inc. Naperville, IL, USA). After fixation, the MG-63 slides were stored in 70% ethanol until use. Cells were first washed separately in TBS for 5 min and then included as a positive control.

#### *Leukocyte immunolocalization*

Sections (5 μm) from formalin-fixed, paraffin embedded biopsies were cut for immunohistochemical localization of (i) macrophages (CD68, DAKO, Code M876); (ii) CD56+ lymphocytes (Zymed, San Francisco, CA, USA); (iii) neutrophil elastase (DAKO Neutrophil Elastase, Code M752). Tissue sections were dewaxed and rehydrated. Non-specific endogenous peroxidase activity was blocked by treatment with 3% hydrogen peroxide in distilled water for 5 min at room temperature. Pre-treatment of the sections was necessary for localization of macrophages and CD56+ lymphocytes as described below.

For macrophage (CD 68) immunostaining, tissue sections were exposed to an enzyme digestion with 0.1% trypsin in 0.1% calcium chloride at pH 7.8. The digestion was conducted at 37°C for 25 min and subsequent enzyme activity removed by washing in tap water.

For CD56+ lymphocyte immunostaining, tissue sections were microwaved at high power in 0.01 M sodium citrate buffer (pH 6.0) for 20 min then allowed to stand for a further 20 min. Sections were washed in buffer prior to a non-immune block.

Thereafter all sections were exposed to a non-immune block with normal horse serum for 20 min at room temperature. Tissue sections were subsequently incubated with the appropriate primary antibody:

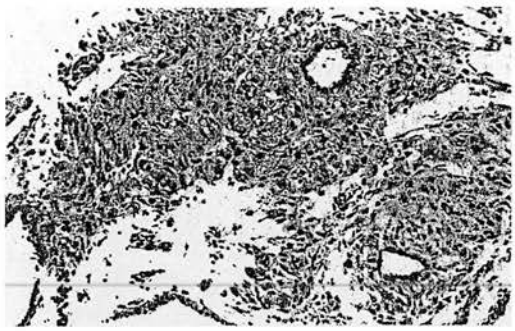

**Figure 1.** Photomicrograph of endometrium exposed to intrauterine levonorgestrel for 3 months. The glands are narrow and inactive and the stroma is typically decidualized. There is a scanty granulated lymphocyte infiltrate. Original magnification ×185.

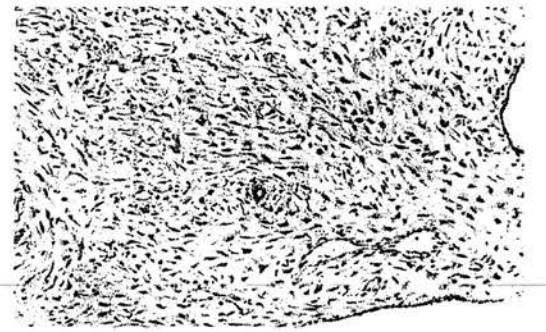

**Figure 2.** An example of the spindle-celled pattern of pseudo-decidualization of the stroma. The central gland is very narrow and inactive. Levonorgestrel intrauterine system *in situ* for 12 months. Original magnification ×185.

(i) macrophage antibody (CD68) dilution 1:50 for 60 min at 37°C;
(ii) CD56 antibody dilution 1:250 for 60 min at 37°C;
(iii) neutrophil elastase antibody dilution 1:50 for 60 min at 37°C.

Sections were labelled with an avidin-biotin-peroxidase detection system (Vector Stain®; Vector Laboratories). Colour development employed diaminobenzidine (DAB) solution for 2–10 min. Subsequently tissue sections were counterstained with haematoxylin, dehydrated and cleared in xylene and mounted in Pertex. Negative controls were conducted by replacing the primary antibody with non-immunized mouse immunoglobulin at the same concentration as the primary antibody.

Immunostaining intensity and distribution of epitopes in all tissue sections were assessed semi-quantitatively, on a four point scale: 0 = no staining, 1 = faint staining, 2 = moderate staining, 3 = intense staining. Scoring was performed blind by two observers. The mean and standard error of mean (±SEM) was calculated. The data were analysed by one-way analysis of variance (ANOVA), using Fisher's PLSD coefficient to assign significance.

## Results

### *Histology*

The LNG–IUS produced widespread morphological changes in the endometrium (Figures 1 and 2). The histological changes were not limited to the contact site although typical contact site changes were observed in the majority of cases. The superficial part of the endometrium formed cushions of rather oedematous, spindle-celled, pseudo-decidualized stroma (Figure 2) and occasionally, microscopic, oedematous, surface micropapillae were seen. In biopsies where the progestational effect was long-standing, the endometrial decidualization remote from the device was spindle-celled and diminished in intensity whilst the decidualization nearest to the device remained more typical with 'rounded' cells rather than spindle cells. Glands in the superficial part of the endometrium were extremely narrow, whilst those in the deeper layers were slightly wider and lined by an epithelium which was cubo-columnar in contrast to the cells lining the superficial glands which were flattened cuboidal. In a small number of biopsies haemorrhagic infarction, necrobiosis or coagulative necrosis was present.

### *Immunohistochemistry*

#### *GM–CSF immunostaining*

Positive immunostaining (brown) for GM–CSF was observed in the cytoplasm of glandular and surface epithelial cells in normal endometrium. In early decidua (Figures 3A and 4) positive immunoreactivity in epithelial and decidualized stromal cells, especially in a perivascular location, was noted. Immunoreactivity tended to be heterogeneous. Regions where decidualization was marked demonstrated strongest immunoreactivity. Strong cytoplasmic glandular and stromal immunoreactivity, particularly in a perivascular location, was also evident following insertion of the LNG–IUS (Figures 3B and 4). There was a significant increase ($P < 0.05$) in GM–CSF immunoreactivity in the stromal compartment of LNG-exposed endometrium at 1, 3, 6 and 12 months post insertion compared with 'pre-insertion' endometrium biopsied in both the proliferative ($P < 0.01$) and secretory phase ($P < 0.05$) of the cycle (Figure 4). Immunoreactivity in normal decidual stromal cells was similar to secretory phase endometrium (see Figure 4, lower panel).

#### *Prolactin-receptor immunostaining*

Minimal positive immunostaining was observed in pre-insertion endometrial biopsies collected in the proliferative phase. However, in pre-insertion endometrial biopsies from the secretory phase, positive immunoreactivity was evident in the cytoplasm of glandular epithelium and in some stromal cells. Biopsies of first trimester decidua displayed strong immunoreactivity in glands and decidualized stromal cells (Figure 3C). Consistent with these features of prolactin receptor immunoreactivity in early decidual tissue, biopsies collected post insertion of the LNG–IUS displayed positive immunostaining both in the glandular epithelium and in pseudo-decidualized stromal cells (Figure 3D). A significant increase ($P < 0.05$) in stromal prolactin receptor immunostaining

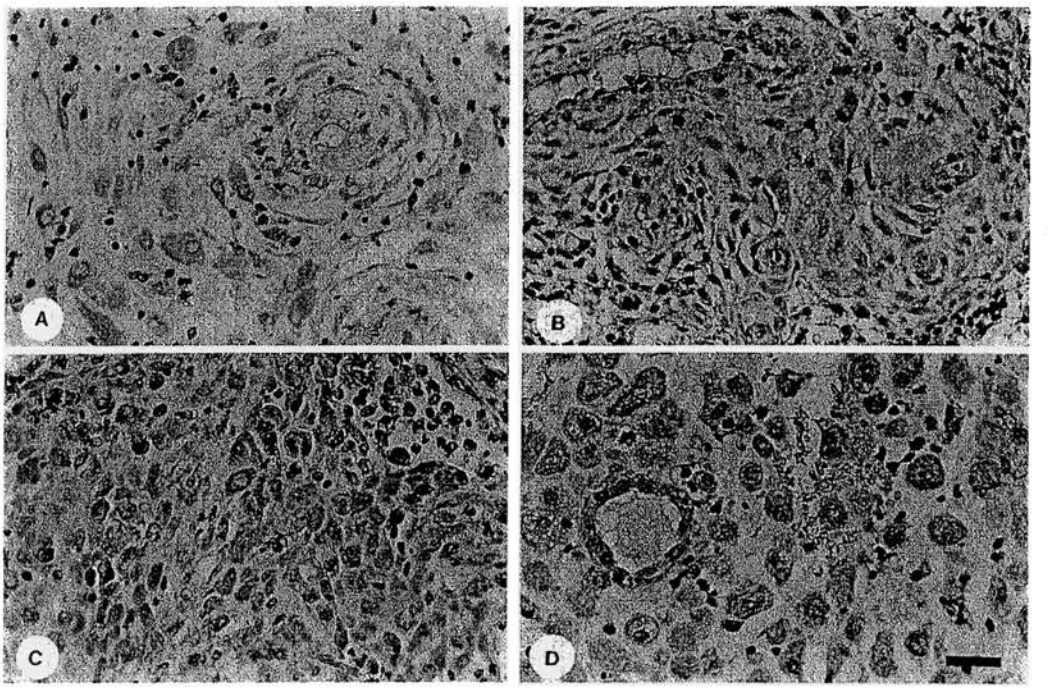


**Figure 3.** (**A**, **B**) Photomicrographs of granulocyte-macrophage colony stimulating factor (GM–CSF) immunostaining. (**A**) First trimester decidua. Positive immunoreactivity (brown staining) is noted particularly in the cytoplasm of large decidualized cells often in a perivascular location. (**B**) Endometrial biopsy from patient 1 month after insertion of levonorgestrel releasing intrauterine system (LNG–IUS). Strong cytoplasmic immunoreactivity is evident in the stroma. (**C**, **D**) Photomicrographs of prolactin receptor immunostaining. (**C**) First trimester decidua. Positive immunoreactivity (brown) is clearly visible in decidualized stromal cells. (**D**) Endometrial biopsy collected 3 months post LNG–IUS insertion displaying positive immunostaining in both glandular epithelium and decidualized stroma. Scale bar = 25 μm.

was evident following insertion of the LNG–IUS (Figure 5, lower panel).

*Leukocyte immunostaining*

Intense positive immunostaining of CD56+ LGL was evident in all endometrial biopsies collected following insertion of the intrauterine system. There was significantly greater ($P < 0.05$) CD56+ immunoreactivity in the stroma of secretory compared to proliferative endometrium, prior to insertion of the LNG–IUS (Figure 6B). The significant increase ($P < 0.05$) was still evident at 1 and 3 months post insertion of the LNG–IUS when compared to proliferative endometrium prior to LNG–IUS insertion (Figure 6B). Strong CD56+ immunostaining was observed however in normal decidua, especially in areas of full decidualization. Positive immunoreactivity for CD68+ macrophages was also obtained in all endometrial biopsies following insertion of the LNG–IUS (Figure 6A). There was a significant increase in macrophage immunostaining between proliferative endometrium pre-insertion and the 1st month post insertion ($P < 0.05$). A significant decrease ($P < 0.05$) in CD68+ macrophage immunoreactivity was noted from 1–12 months post insertion. There was negligible immunostaining for neutrophil elastase (polymorphonuclear leukocyte marker) in all post insertion endometrial biopsies (data not shown).

## Discussion

In order to elucidate further local mechanisms governing endometrial function with local intrauterine delivery of levonorgestrel, the present study has reported histological features consistent with decidualization. We have observed a significant increase in GM–CSF immunoreactivity, particularly in the decidualized stromal cells observed in LNG exposed endometrium, plus glandular and stromal prolactin receptor expression and an infiltrate of CD56+ large granular lymphocytes and CD68+ macrophages. We are unaware of any previous reports which have documented longitudinally both morphological and functional observations in endometrium exposed to local intrauterine LNG delivery.

The endometrial morphological features following intrauterine levonorgestrel delivery are typical of those seen in long-term users of a progestogen (Silverberg *et al.*, 1986; Buckley and Fox, 1989). The features of pseudo-decidualization closely resembled the morphology of early pregnancy decidua.

The progestational effects observed in this study occurred throughout the endometrium and are consistent with an earlier report (Nilsson *et al.*, 1978), and were not limited to the immediate vicinity of the device. The endometrial biopsies

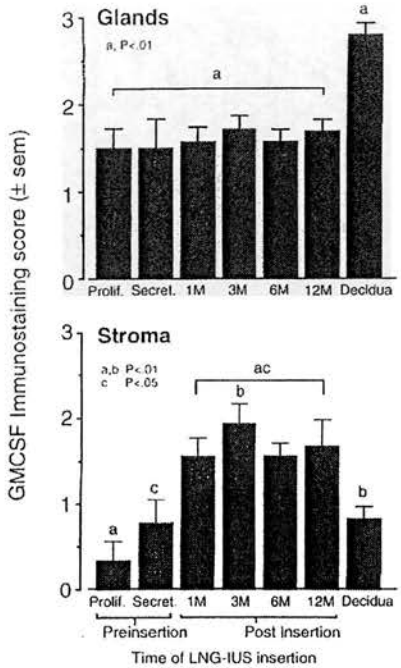


**Figure 4.** Granulocyte-macrophage colony stimulating factor (GM–CSF) immunostaining scores (mean ± SEM) in endometrial glands (upper panel) and stroma (lower panel) prior to and following insertion of levonorgestrel releasing intrauterine system (LNG–IUS). Prolif. = proliferative phase, Secret. = secretory phase, M = months.

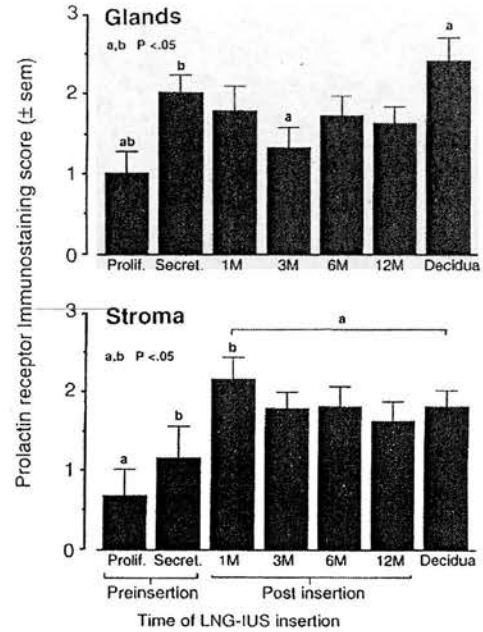


**Figure 5.** Prolactin receptor immunostaining scores (mean ± SEM) in endometrial glands (upper panel) and stroma (lower panel) prior to and post insertion of a levonorgestrel releasing intrauterine system (LNG–IUS).

examined in the present study did not display the micropolyps described by Silverberg *et al.* (1986) where the median duration of use was 48 months and women using a device releasing 20 μg daily were all examined after at least 12 months of use. The lack of observation of micropolyps in our study may be due to the fact that the levonorgestrel intrauterine system had only been *in situ* for up to 12 months.

In a few biopsies haemorrhagic infarction, necrobiosis and coagulative necrosis were present. These features are indicative of spontaneous tissue breakdown but differ from that seen in normal menstruation, in that the features were usually focal or multifocal. All subjects in this study had recorded details of daily bleeding (if present) for the full 12 months study period. On review, the biopsies with evidence of spontaneous tissue breakdown were not from subjects who had described break-through bleeding (unpublished data).

Any agent which modifies endometrial morphology is likely also to modify the normal intrauterine processes regulating function. The stromal GM–CSF immunoreactivity in the local levonorgestrel treated endometrium closely resembled GM–CSF immunostaining in the epithelial and stromal cells of first trimester decidua. Particularly of note was the localization of immunostaining to large perivascular decidualized cells. Appreciable amounts of GM–CSF are known to be produced by first trimester decidua (Jokhi *et al.*, 1994) and a potential role in leukocyte recruitment has been proposed (Robertson and Seamark, 1992).

Prolactin receptor protein has been immunolocalized to the glandular epithelium and stromal cells of pseudo-decidualized endometrium following intrauterine levonorgestrel delivery. Our observation is consistent with data from our group (Jones *et al.*, 1998) concerning expression of the prolactin receptor in both normal endometrium and first trimester decidua. Locally derived growth factors and cytokines are likely to regulate prolactin receptor expression (Gu *et al.*, 1994), and the detection of strong immunoreactivity for the receptor in both epithelium and stroma in pseudo-decidualized endometrium suggests a paracrine role for prolactin.

The pseudo-decidualized endometrium associated with local levonorgestrel delivery displayed a significant increase in CD56+ LGL when compared with proliferative phase endometrium and has a persistent population of macrophages. Normal decidua has a similar leukocyte population (Loke and King, 1995). The mode of recruitment of these cell types remains under investigation, although, under the influence of progesterone, neither cell type to date has been reported to express sex steroid receptors (King *et al.*, 1996). Local intrauterine levonorgestrel delivery results in a down-regulation of stromal progesterone receptors (Critchley *et al.*, 1998) at a time where, in the current study, we have observed strong prolactin receptor immunoreactivity that increased significantly 1 month post insertion of the LNG–IUS.

From the above data it must be concluded that the stromal

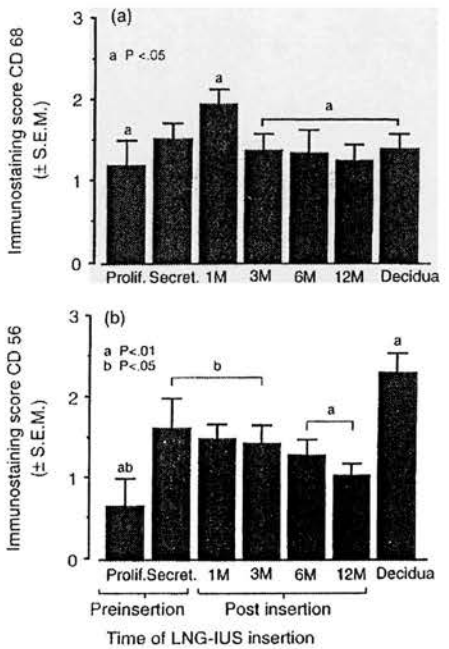


**Figure 6.** Mean (± SEM) immunostaining scores for (**a**) macrophages (CD68+) and (**b**) large granular lymphocytes (CD56+) in endometrial stroma before and after exposure to intrauterine levonorgestrel.

compartment of the endometrium does indeed undergo changes consistent with decidualization for at least up to 12 months post insertion of LNG–IUS. Previous examination of the state of the endometrial stroma in progestin-only contraceptive users was limited (Findlay, 1996). Furthermore, it has been suggested (Findlay, 1996) that there may be a short phase of decidualization following commencement of the method. In this study evidence is presented that GM–CSF and prolactin receptor proteins immunolocalize to the pseudo-decidualized cells in a similar manner to the true decidual cells of first trimester pregnancy. It is notable that GM–CSF protein localized particularly to large decidualized perivascular cells. Findlay (1996) has noted that in progestin exposed endometrium the decidualized cells may produce factors not normally associated with true decidualized cells which may have the potential to be detrimental to blood vessels.

It is worth noting that in normal decidua immunoreactivity was heterogeneous, and was most marked for GM–CSF, prolactin receptor and CD56 where decidualization was apparent. In these early pregnancy biopsies some regions still displayed a marked glandular morphology. It is recognised that during the first trimester, two histologically distinguishable zones may be observed (Bell, 1991).

The presence of a marked and persistent population of CD56+ LGL is also consistent with the observation that uterine LGL are the predominant lymphocytes reported in first trimester decidua (Loke and King, 1997). Furthermore, in this study macrophages were evident throughout the 12 months following insertion of a LNG–IUS. In this context Clark *et al.* (1996) reported a reduced frequency of CD68+ cells in the atrophic endometrium of Norplant® users (sub-dermal levonorgestrel). The number of CD68+ cells was significantly increased in those women using Norplant with abnormal bleeding. In the context of the present study there was a significant increase in macrophage immunoreactivity at 1 month post LNG–IUS insertion and proliferative phase endometrium. Interestingly, thereafter a significant decrease in macrophage immunostaining was observed between 1 and 12 months following insertion of LNG–IUS. No formal quantification of immunostaining was undertaken due to the small size of many of the later biopsies, and hence the description was subjective.

Bleeding disorders remain a major problem and a primary reason for discontinuation of progestin-only methods of contraception (Findlay, 1996). A previous irregular menstrual history has been raised as a potential contributing factor to bleeding disorders. In the present study all women recruited described a regular bleeding history. Many of them went on to experience irregular bleeding with the LNG–IUS *in situ*. A minority ($n$ = 4) also described heavy loss. Nine out of 14 women (64%) experienced light menstrual blood loss each month and only one subject achieved amenorrhoea with the LNG–IUS (unpublished data). Despite detailed scrutiny of the several end points in this study, no correlation was established with the menstrual bleeding patterns described by the subjects.

A detailed understanding of the local endometrial mechanisms which are disturbed by the presence of high dose intrauterine progestagen are also important with respect to the contraceptive action of the LNG–IUS. Recently Mandelin *et al.* (1997) described inappropriate glycodelin A mRNA and protein expression before and at mid cycle in women using a LNG–IUS. This untimely production of glycodelin A has been implicated in the contraceptive action of the LNG–IUS. In this context glycodelin A is usually absent from the endometrium in the proliferative and immediate postovulatory phases, i.e. at a time when glandular progesterone receptor expression is maximal. It is interesting to note that the inappropriate production of glycodelin A coincides with the down-regulation of progesterone receptor reported (Critchley *et al.*, 1998) with intrauterine levonorgestrel administration.

In summary, the present study has described features consistent with endometrial decidualization in the presence of an intrauterine levonorgestrel-releasing system. It is not possible to determine whether these decidualized cells are 'true decidual cells' (Findlay, 1996) although several of the features described herein are almost indistinguishable from normal decidua. Further study of the decidualized nature of the stromal cells in the levonorgestrel exposed endometrium should contribute to a greater understanding of the mechanisms responsible for break-through bleeding, a major reason for discontent with progestin-only contraception.

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# Regulation of matrix metalloproteinase-9 in endometrium during the menstrual cycle and following administration of intrauterine levonorgestrel

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**Remodelling of endometrial tissues is fundamental to the cyclical changes that occur during the menstrual cycle, implantation and, in the absence of pregnancy, at menstruation. The enzyme matrix metalloproteinase-9 (MMP-9) is recognized as important in these processes but its regulation is not well defined. These studies have demonstrated that MMP-9 activity is present in the endometrium and exhibits cyclical changes in its distribution in the glandular and stromal cells. MMP-9 protein is present throughout the cycle with highest expression, as determined by semi-quantitative analysis of specific MMP-9 immunoreactivity, in glandular cells during the mid secretory phase. A similar distribution was observed in first trimester decidua. In women with a levonorgestrel intrauterine system (LNG-IUS), which delivers high local concentrations of progestagen to the uterine cavity, MMP-9 is highly expressed in both endometrial glandular and stromal cells, and in the vasculature (in endothelial and perivascular cells). It can be concluded that MMP-9 is stimulated directly or indirectly by progesterone. Furthermore, MMP-9 may play a role in the remodelling of the endometrium that occurs during the menstrual cycle and in the aetiology of the morphological changes and breakthrough bleeding associated with long-term progestagen administration via a LNG-IUS.**

*Key words:* contraception–LNG/endometrium/matrix metalloproteinases/menstruation/tissue remodelling

## Introduction

Tissue remodelling in the uterus is an important process during the normal menstrual cycle for the sequential destruction and reconstruction of the endometrial functionalis, for implantation processes and subsequent development of the placenta and fetal–maternal interface (Hulboy *et al.*, 1997). The matrix metalloproteinases (MMP) are a family of zinc-dependent enzymes that are important for these tissue remodelling processes by degrading components of the extracellular matrix (ECM), basement membrane and interstitial matrix (Rawdanowicz *et al.*, 1994). To date there have been 16 distinct MMP cloned and characterized in the human and the family member MMP-9 is a 92 kDa gelatinase enzyme that degrades components of the extracellular matrix and basement membrane components, specifically, collagens IV and V, elastin and gelatin (Hulboy *et al.*, 1997). MMP-9 is expressed in the uterus and cellular sources include endometrial glandular and stromal cells, macrophages, neutrophils and first trimester cytotrophoblast cells (Jeziorska *et al.*, 1996; Salamonsen and Woolley, 1996; Bischof *et al.*, 1998). The gelatinase MMP-2 is also expressed and secreted by human endometrium (Irwin *et al.*, 1996; Salamonsen *et al.*, 1997). There is increasing evidence for a role for MMP in the tissue remodelling events of implantation and, in the absence of pregnancy, subsequent menstruation (Rodgers *et al.*, 1994; Marbaix *et al.*, 1995; Salamonsen and Woolley, 1996).

The regulation of MMP-9 is not well understood but it is controlled, at least in part, by progesterone. Maximal intraluminal secretion of MMP-9 by glandular epithelial cells occurs at a time when progesterone concentrations are highest during the 'implantation window' of early to mid secretory phase (Jeziorska *et al.*, 1996) although its release from endometrial explants is inhibited by progesterone *in vitro* (Rodgers *et al.*, 1994). This control of MMP-9 and indeed uterine function by progesterone is clearly complex, demonstrated by these differing responses found *in vivo* and *in vitro*. A compounding factor of this regulation is that the two isoforms of the progesterone receptor (PR), $PR_A$ and $PR_B$, are present in epithelial and stromal cells during the proliferative phase. In the secretory phase both receptor subtypes decline in the glandular compartment and $PR_B$ decreases in the stroma (Wang *et al.*, 1998).

The levonorgestrel-releasing intrauterine system (LNG-IUS; Leiras Oy, Finland) is associated with a 97% reduction in menstrual blood loss (Andersson and Rybo, 1990; Milson *et al.*, 1991). However, the most common indication for discontinuation of use of this method and indeed other progesterone-only systems of contraception, with its associated dramatic reduction in menstrual bleeding, is the occurrence of the troublesome side-effect of unpredictable breakthrough bleeding (Findlay, 1996). The long-term administration of intrauterine levonorgestrel results in features of altered morphology and function of the endometrium (Critchley *et al.*, 1998a) and down-regulation of receptors for oestrogen and both isoforms of the progesterone receptor (Critchley *et al.*, 1998b). The paracrine mechanisms which account for the disturbance in bleeding patterns associated with intrauterine levonorgestrel delivery remain to be elucidated. Endometrium obtained from women using a LNG-IUS provides an opportunity to study the effect of high-dose local progestagen delivery upon endometrial development. The aims of this study were to investigate the

control of MMP-9 in the endometrium during the menstrual cycle and to elucidate further its regulation by local intrauterine LNG *in vivo*.

## Materials and methods

### *Patients and tissues*

Normal endometrium was collected from women ($n$ = 40) aged 38 years (median, range 25–47) undergoing minor gynaecological procedures (including laparoscopic sterilization, diagnostic laparoscopy for pelvic pain, endometrial sampling for regular but dysfunctional uterine bleeding) collected by Pipelle suction curette (Laboratoire CCD, Paris, France). All women described regular cycles (25–35 days). Endometrial samples were designated as menstrual, early proliferative, mid proliferative, late proliferative, ovulatory, early secretory, mid secretory and late secretory phase ($n$ = 5 for each stage of cycle). Dating was based on the histological criteria of Noyes *et al.* (Noyes *et al.*, 1950) and all biopsies were consistent with the date of the last menstrual period. No subject had received exogenous hormones or had used an intrauterine device in the 3 months prior to biopsy. A 10 ml sample of venous blood was collected at the time of each endometrial biopsy for estimation of serum oestradiol and progesterone concentrations by radioimmunoassay. Circulating concentrations of serum oestradiol and progesterone at the time of endometrial biopsy in women using a LNG-IUS have been previously reported (Critchley *et al.*, 1998b) and reflect continued ovarian activity in subjects with a LNG-IUS *in situ*.

Endometrial tissue was collected from 14 women aged between 32 and 48 years (median 37) who provided informed consent for an endometrial biopsy prior to, and following, insertion of an LNG-IUS. All participants were fertile, described regular menstrual cycles (cycle length 25–35 days) and were not using hormonal or intrauterine contraception in the 6 months prior to inclusion in the study. The indication for insertion of the LNG-IUS was either for contraception, often also in association with heavy menses ($n$ = 10), or heavy menstruation ($n$ = 4). The study was longitudinal with each subject acting as her own control. Seven subjects underwent a pre-insertion endometrial biopsy in the proliferative phase and seven subjects in the secretory phase of the menstrual cycle prior to insertion of the LNG-IUS. The stage of the cycle prior to LNG-IUS insertion was defined according to the criteria of Noyes *et al.* (1950). All biopsies were performed in an outpatient setting with a Pipelle suction curette. Subsequent endometrial biopsies were collected 1, 3, 6 and 12 months following insertion of the LNG-IUS. Once the LNG-IUS was *in situ*, the histological appearance of the endometrium samples was indistinguishable whether collected in the follicular or luteal phase of the cycle, hence data at time periods of 1, 3, 6 and 12 months were pooled. The sex steroid receptor expression in this longitudinal series of biopsies has been previously reported (Critchley *et al.*, 1998b).

A further five women (8–10 weeks amenorrhoea) provided decidual tissue at the time of planned surgical termination of pregnancy. Decidual biopsies were collected following dilatation of the cervix and curettage of the uterine wall prior to vacuum aspiration of products of conception. Placental biopsies were also collected at this time. Decidual and placental villous biopsies were immunostained with a monoclonal antibody against cytokeratin (Dako MO821, High Wycombe, Bucks, UK) to confirm absence of trophoblast tissue (decidua parietalis).

Ethical approval for this study was granted by the Lothian Research Ethics Committee (reference: 1702/94/6/44 and 1702/93/6/73) and all tissue samples were obtained with informed written consent from all patients.

For zymography, endometrium was snap-frozen immediately after collection and stored at −70°C. For immunohistochemistry, all endometrium and decidua samples were fixed overnight in 10% neutral buffered formalin at 4°C, rinsed and stored in 70% ethanol and thereafter routinely waxed embedded. Sections (5 µm) were cut and mounted on 3-aminopropyltriethoxysilane-coated slides (Sigma, St Louis, MO, USA) for routine histopathology (haematoxylin and eosin staining) and immunolocalization of MMP-9.

### *Zymography*

Gelatinase activity was detected by zymography using methods described previously with minor modifications (Rawdanowicz *et al.*, 1994). Briefly, tissues were homogenized [extraction buffer 0.2% sodium dodecyl sulphate (SDS) in $H_2O$; 100 µg tissue wet weight/ml buffer] and protein concentrations measured. Samples were separated (50 µg protein loaded) by SDS–polyacrylamide gel electrophoresis (PAGE) using gels (7.5%) containing gelatin (1 mg/ml) using non-reducing conditions. Gels were washed (2.5% Triton X-100) and incubated in zymography digestion buffer (50 mM Tris, 0.2 M NaCl, 5 mM $CaCl_2$, 1 µM $ZnCl_2$, 0.02% Brij-35, pH 7.6) at 37°C for 18 h. Gels were then stained (0.5% Coomassie blue R250 in 30% methanol/10% glacial acetic acid) at 23°C for 3 h, destained (staining solution omitting the Coomassie blue) to reveal the discrete areas where gelatinase activity had hydrolysed the substrate.

### *Immunolocalization of MMP-9*

Immunoreactive MMP-9 was localized using standard techniques. In brief, sections were dewaxed, rehydrated and endogenous peroxidase activity blocked by incubation with $H_2O_2$ (3% v/v for 20 min; Sigma). Sections were washed extensively and a further blocking step of normal horse serum (5% v/v for 20 min) applied. Tissue sections were then incubated (17 h at 4°C) with the primary mouse monoclonal antibody (2 µg/ml final concentration) raised against a peptide sequence corresponding to amino acids 624 to 644 in the carboxy-terminal domain of MMP-9 (Insight Biotechnology Ltd, Wembley, Middlesex, UK). The primary antibody was detected using a biotinylated horse anti-mouse antibody and an avidin–peroxidase complex (Vector Laboratories, Burlinghame, CA, USA), then visualized with 3,3′-diaminobenzidine as chromagen (Vector) according to the manufacturers instructions. Sections were counterstained, dehydrated and mounted.

The specificity of the MMP-9 antibody used for immunohistochemistry was confirmed using immunoblotting techniques. In brief, conditioned medium samples collected from endometrial explants were dialysed and concentrated by lyophilization. Secreted proteins were separated by PAGE (7.5% gels) and transferred to a nitrocellulose membrane (0.45 µm pore size; Biorad, Hemel Hempstead, Herts, UK) by wet blotting. The membrane was blocked with 5% bovine serum albumin, before application of the MMP-9 antibody, which was detected using the same methods used for immunohistochemistry.

Negative controls were performed by replacing the primary antibody with non-immune mouse immunoglobulin at a concentration of 1:500 in diluted horse serum (purified MMP-9 antigen was not available). Sections of placenta collected at term were used as a positive control, which demonstrated strongly positive and consistent immunolocalization of MMP-9 in cytotrophoblast and extravillous trophoblast cells throughout all the experiments performed, as described previously (Riley *et al.*, 1997).

### *Scoring and analysis of immunoreactivity*

Immunostaining intensity and proportion of positive immunoreactivity of epitope in all tissue sections was assessed semi-quantitatively, on a 4-point scale. A score of 3 indicated intense immunostaining of

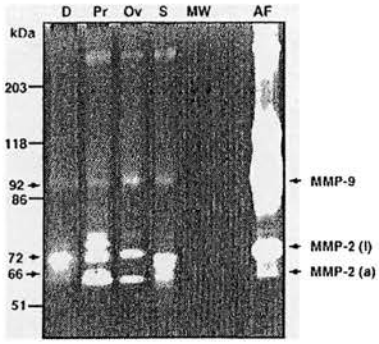


**Figure 1.** Gelatin zymogram demonstrating matrix metalloproteinase (MMP)-9 (92 kDa gelatinase B) and MMP-2 (72 kDa gelatinase A) in homogenates of endometrium from the proliferative (Pr), ovulatory (Ov) and secretory (S) phases of the menstrual cycle and decidua collected from the first trimester of pregnancy (D). Amniotic fluid (AF) collected at term after spontaneous delivery was used as a positive control.

>95% for the cell types, that is, glandular or stromal cells examined. Scores of 1 and 2 indicated weak or moderate immunostaining, respectively. A score of zero indicated an absence of immunoreactivity. The scoring was performed blind by a single observer, without prior knowledge of phase of the menstrual cycle. The mean ± SEM was calculated. The data were analysed by one-way analysis of variance (ANOVA) using Fisher's PLSD (protected least significant difference) coefficient to assign significance.

## Results

### *MMP-9 activity in endometrium and decidua*

Gelatin zymography demonstrated that MMP-9 activity, corresponding to 92 kDa, was detectable in endometrium tissue samples from throughout the menstrual cycle and also from decidua collected during the first trimester of pregnancy (Figure 1). In addition, MMP-2 enzyme activity (corresponding to 72 kDa) was evident in endometrium and decidual samples (see Figure 1). The specificity of this activity as being derived from MMP was confirmed by incubation with EDTA (5 mM) or *o*-phenanthroline (2.5 mM), with both treatments inhibiting activity of all bands (data not shown).

### *Immunolocalization of MMP-9 during the menstrual cycle*

The specificity of the MMP-9 antibody was confirmed by immunoblot (Figure 2). A single band at the expected 92 kDa molecular weight was identified as a secreted product in culture medium conditioned by tissue explants of endometrium. This aligned with the strong single band in the amniotic fluid positive control.

Positive immunoreactivity for MMP-9 was predominantly visualized in the cytoplasm of the majority of glandular epithelium in both the proliferative, secretory and menstrual phases of the cycle (Figure 3a–c). In endometrial stromal cells, a heterogeneous distribution of lower intensity MMP-9 immunoreactivity was observed, with immunostaining more marked in the secretory phase (Figure 3b), especially in the

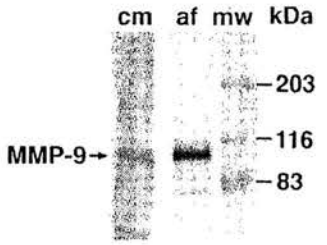


**Figure 2.** Immunoblot demonstrating the presence of matrix metalloproteinase (MMP)-9 immunoreactivity, identified at 92 kDa molecular weight (mw), in samples of conditioned medium collected from explants of endometrium (cm) and also as a positive control in amniotic fluid (af) obtained at active labour at term.

late secretory stage. The intensity of MMP-9 immunostaining expressed by semi-quantitative analysis during the proliferative and secretory phases of the cycle is demonstrated in Figure 4. There was no significant difference in the intensity or distribution of MMP-9 immunoreactivity between these phases of the menstrual cycle. In the endometrial vasculature, MMP-9 immunoreactivity was localized in endothelial cells and also in perivascular cells in some vessels throughout the menstrual cycle (Figures 3a–c). All negative control sections consistently demonstrated no positive staining (representative section, Figure 3d). All biopsies collected during the normal menstrual cycle were from the functionalis layer, since a Pipelle sampling device (suction curette) was employed.

### *Immunolocalization of MMP-9 in decidua and placenta during early pregnancy*

MMP-9 immunoreactivity was localized in decidual tissue in a similar pattern of distribution and intensity to that seen in the mid and late secretory phases of the cycle (Figure 3f). Maximal MMP-9 immunostaining was present in glandular epithelial cells, whereas in stromal cells staining was heterogeneous from strong to less intense and absent. The localization of MMP-9 in the vasculature was similar to that found during the menstrual cycle, evident in endothelial and some perivascular cells (Figure 3f). In placenta, MMP-9 was localized in villous tissue predominantly in syncytiotrophoblast, but not in cytotrophoblast cells (Figure 3g).

### *Immunolocalization of MMP-9 in endometrium exposed to intrauterine levonorgestrel*

Endometrial biopsies collected prior to insertion of the LNG-IUS demonstrated normal morphology consistent with features of the proliferative or secretory phase described, and localization of MMP-9 immunoreactivity was comparable to normal tissues collected from the same stage of the cycle as reported above.

All subjects in whom biopsies were collected in the follicular phase (proliferative histology) had circulating progesterone concentrations of ≤10 nmol/l (range 0–10, 3.4 ± 1.9 nmol/l, mean ± SEM). Subjects in whom biopsies were collected in the luteal phase (secretory histology) had serum progesterone concentrations between 6 and 29 nmol/l (17.7 ± 2.9). Post

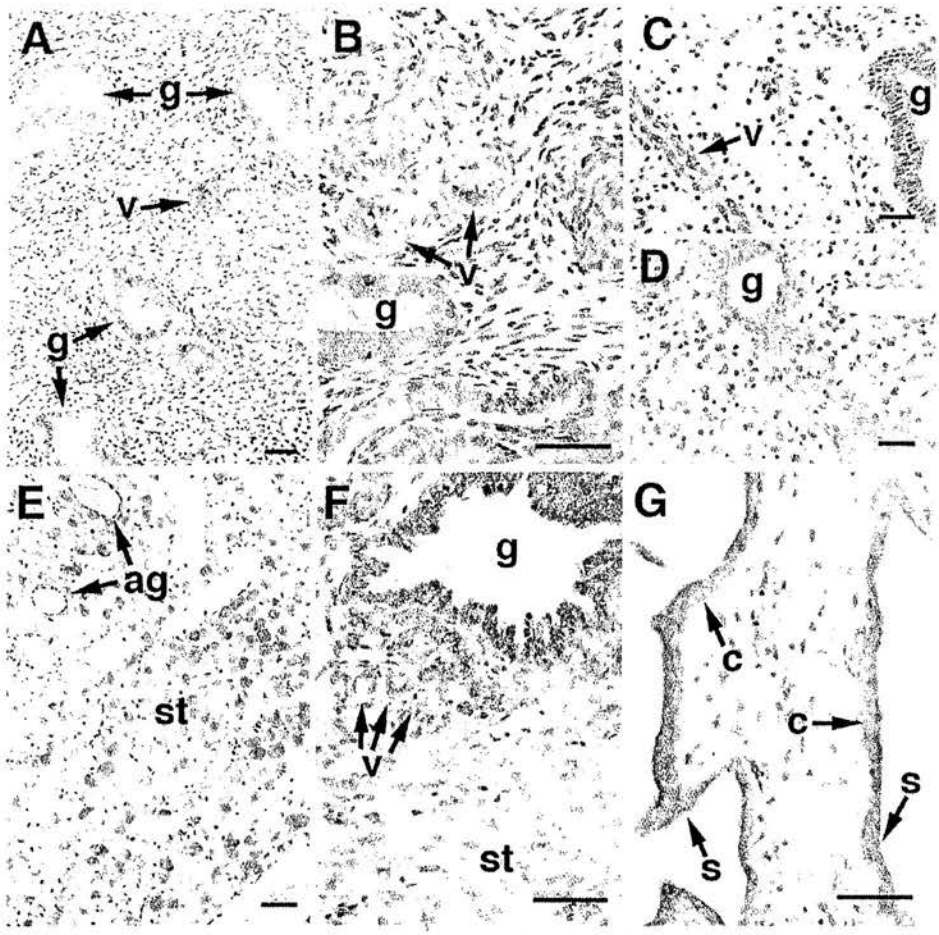


**Figure 3.** Localization of matrix metalloproteinase-9 immunoreactivity in endometrium collected from the menstrual cycle in the (**A**) proliferative phase, predominantly in glandular epithelium, (**B**) early secretory phase, predominantly in glandular epithelium, in the vasculature and in some stromal cells and (**C**) during the menstrual phase in glandular epithelium and vasculature (note stromal breakdown); (**D**) a representative negative control section demonstrating no positive non-specific staining; (**E**) from a woman with a levonorgestrel intrauterine system *in situ* strongly in decidualized stromal cells with less immunostaining in atrophic glands (**F**) in decidua collected from the first trimester of pregnancy in glandular epithelium, stromal cells and vasculature, and (**G**) in placenta in villous tissue in syncytiotrophoblast. v = vasculature; s = syncytiotrophoblast; c = cytotrophoblast; g = glandular epithelium; ag = atrophic gland; st = stromal cells. All scale bars = 50 μm.

insertion of the LNG-IUS serum progesterone and oestradiol concentrations were within normal follicular and luteal concentrations as expected, and have been previously published (Critchley *et al.*, 1998b).

Following insertion of the LNG-IUS, endometrial morphology was modified with widespread pseudo-decidualization evident in all biopsies. MMP-9 immunoreactivity remained marked in the glandular compartments, although it became less evident with increased atrophy of these glands (Figure 3e). In contrast to the normal cycle, following insertion of the LNG-IUS regardless of the time period at which the biopsy was taken, intense MMP-9 immunoreactivity was present in the stromal cells of all biopsies (Figure 3e). There was a significant ($P < 0.05$) increase in MMP-9 immunoreactivity in the endometrium collected following insertion of the LNG-IUS, compared with biopsies collected in both the proliferative and secretory phases of the cycle (Figure 5).

## Discussion

In normal endometrium MMP-9 enzyme activity is present throughout the menstrual cycle. MMP-9 immunoreactivity was localized predominantly in glandular epithelial cells with the highest quantities observed in the mid to late secretory and

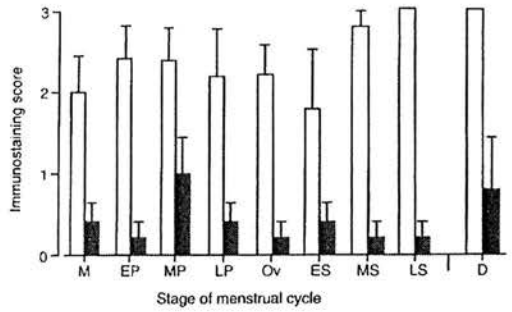


**Figure 4.** Immunostaining scores assessed by semi-quantitative analysis of matrix metalloproteinase-9 immunoreactivity in glands and stromal cells of endometrium throughout the early (E) mid (M) and late (L) stages of the proliferative (P), ovulatory (Ov), secretory (S) and menstrual (M) phases of the menstrual cycle D = decidua from early pregnancy ($n$ = 5 tissue samples collected from different women at each time point). Open bars = glands; solid bars = stromal cells.

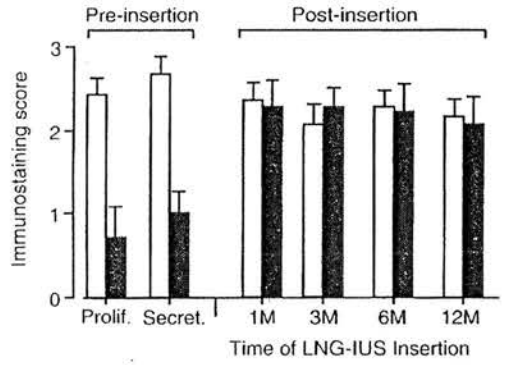


**Figure 5.** Immunostaining scores assessed by semi-quantitative analysis of matrix metalloproteinase-9 immunoreactivity in glands and stromal cells of endometrium collected from women in the proliferative (prolif) and secretory (secret) phases of the menstrual cycle prior to and 1, 3, 6 and 12 months (M) after the insertion of a LNG-IUS. Open bars = glands; solid bars = stromal cells.

peri-menstrual phases of the cycle. In decidua in early pregnancy, MMP-9 was present in glands and also in decidualized stromal cells. These findings indicate a role for MMP-9 in the remodelling processes that occur during menstruation and at implantation (Marbaix *et al.*, 1992; Salamonsen and Woolley, 1996) Following intrauterine delivery of levonorgestrel by a LNG-IUS there was a significant increase in endometrial stromal MMP-9 immunoreactivity, indicating that progesterone may be involved, at least indirectly, in the control of MMP-9 expression. In addition, MMP-2 enzyme activity is present in endometrium obtained throughout the menstrual cycle and during early pregnancy, as demonstrated by zymography.

The findings in this study demonstrate that in the normal menstrual cycle MMP-9 protein was immunolocalized to glandular epithelial cells throughout the menstrual cycle with maximal intensity in the glandular epithelium. A previous study which examined MMP-9 localization in human endometrium (Jeziorska *et al.*, 1996) showed similar findings in the proliferative phase. As in this present study, intraluminal secretion was evident with peak concentrations in glandular secretion and uterine fluid at the peri-implantation period. However, Jeziorska *et al.* (Jeziorska *et al.*, 1996) observed a disappearance of MMP-9 immunoreactivity in the late secretory phase and perimenstrually, contrary to our findings. Furthermore, Rodgers *et al.* (Rodgers *et al.*, 1994) reported that expression of MMP-9 mRNA was most evident in late secretory and menstrual endometrium. Such observations support a role for MMP-9 in remodelling of the extracellular matrix and in the production of glandular secretions which may be associated with blastocyst recognition and implantation. In stromal cells, MMP-9 immunoreactivity was generally low throughout the cycle with only an increase in the late secretory phase, where it may have a role in the profound changes in morphology during decidualization as well as at menstruation. By dual immunolocalization, Jeziorska *et al.* (Jeziorska *et al.*, 1996) noted that MMP-9 immunoreactivity was present in polymorphonuclear leukocytes and macrophages, with little MMP immunoreactivity in stromal cells and resident leukocytes, including mast cells. The observation of MMP-9 expression in subpopulations of leukocytes within the endometrium at critical times, for example pre- and peri-menstrually, is consistent with a role for these cell types as a source of endometrial MMP-9 expression (Jeziorska *et al.*, 1996).

Immunoreactive MMP-9 was localized in the endometrial vasculature in endothelial and perivascular cells throughout the menstrual cycle and may play a role in the angiogenesis and development of the vasculature, as well as the breakdown of vessels during menstruation. Roberts *et al.* (Roberts *et al.*, 1992) in an electron microscopy study demonstrated extensive breakdown of the vascular basal lamina prior to menstruation. Specifically in the pre-menstrual period structural interactions between endothelial and neighbouring pericytic cells are impaired. This endothelial cell hypertrophy evident in the luteal phase of the cycle has been attributed to rising concentrations of progesterone in combination with oestrogen. In late secretory endometrium the necrosis evident in stromal tissues is distinct from that in capillary endothelial cells (Roberts *et al.*, 1992).

In women using an intrauterine device (IUD), overall secretion of gelatinase activity increases throughout the cycle, with increased MMP-9 secretion during the proliferative phase (Martelli *et al.*, 1993). This activity was attributed to bone marrow-derived cells, in agreement with the findings of Jeziorska *et al.* (Jeziorska *et al.*, 1996). This may be involved in the rise in blood loss at menstruation associated with IUD use.

The role of progesterone in the regulation of endometrial MMP-9 expression is unclear. These and previous studies (Jeziorska *et al.*, 1996) have demonstrated that glandular MMP-9 production increases at a time when progesterone also increases, but it is maintained when progesterone concentrations fall in the perimenstrual period. The LNG-IUS releases 20 μg of levonorgestrel daily directly to the uterine cavity and this results in the typical morphological changes in the endometrium associated with long-term use of a progestagen

(Silverberg *et al.*, 1986; Buckley and Fox, 1989) including pseudo-decidualization resembling the morphology observed during the first trimester (Critchley *et al.*, 1998a). This study has shown an increased MMP-9 immunoreactivity in association with this decidualization within one month post insertion of LNG-IUS which persisted throughout the study period following LNG-IUS insertion. This high expression of MMP-9 may be involved in the tissue remodelling that occurs during reduction of the functionalis layer of the endometrium with long-term treatment with progestagen contraceptives (Marsh *et al.*, 1995). MMP-9 may also have a role in the aetiology of breakthough bleeding (since MMP-9 is localized in the vasculature) which is the major problem with this contraceptive method.

In women using a LNG-IUS, both isoforms of the progesterone receptor ($PR_A$ and $PR_B$) are down-regulated and there is a reduction in some progesterone-dependent endometrial markers (Critchley *et al.*, 1998b) including glycodelin (Mandelin *et al.*, 1997). Interestingly $PR_B$ isoform is the more suppressed of the two subtypes and thus $PR_A$ is likely to be the subtype that mediates long term levonorgestrel action in the endometrium (Critchley *et al.*, 1998b; Wang *et al.*, 1998). Similarly, studies *in vitro* demonstrate that after several days in culture, more MMP-9 is secreted by stromal than epithelial cells in culture (Salamonsen *et al.*, 1997) and progesterone withdrawal is the optimal stimulus for inducing MMP-9 expression in these cells. Nevertheless, this study and others (Jeziorska *et al.*, 1996) indicate that the stromal cells are not the principal source of MMP-9 during the normal menstrual cycle and that these alterations in stromal cell MMP-9 expression do not occur *in vivo* during the normal cycle but are a response to decidualization during early pregnancy or exogenous progestogen treatment, or to in-vitro culture (Salamonsen *et al.*, 1997). There is recent evidence for the cell specificity of progesterone receptor regulation (Tseng and Zhu, 1997) with progestin stimulating progesterone receptor mRNA in cultured human endometrial stromal cells. This stromal–decidual cell system is novel in that progestin induces numerous factors, such as specific cytokines and prolactin, that in turn regulate the concentration of progesterone receptor. Hence differential pathways are involved in the regulation of PR isoforms in endometrial stromal cells.

MMP are also controlled after secretion by inhibition of enzyme activity by endogenous tissue inhibitors of metalloproteinases (TIMP). TIMP-1, -2 and -3 are localized in endometrium and are secreted by decidualized stromal cells in culture, but it is proposed that they are not regulated during the menstrual cycle and their role would appear to be maintenance of tissue integrity (Hulboy *et al.*, 1997; Zhang and Salamonsen, 1997).

In placenta during the first trimester, MMP-9 is localized in syncytiotrophoblast, but not cytotrophoblast, cells. However, cytotrophoblast cells collected at this time and maintained in culture secrete MMP-9, although this may be due to alterations in phenotype *in vitro* (Librach *et al.*, 1994). At this stage, interactions between trophoblast and decidua are important for the establishment of the fetal–maternal interface. An as yet unidentified factor in medium conditioned by decidualized stromal cells stimulates gelatinase activity and MMP-9 release by first trimester trophoblast cells (Bischof *et al.*, 1998). This may be an important component of the control of trophoblast invasion at this time.

The antibody used in this study does not distinguish between the latent and active forms of MMP-9, so care must be taken in the interpretation of these data, although the major form of MMP-9 detected by zymography was the latent 92 kDa form. The concentrations of total protein as assessed here by semi-quantitative analysis of immunohistochemistry does not establish enzyme activity within tissues.

In summary, this study confirms that MMP-9 activity is present in normal endometrium and decidua with an increased MMP-9 expression in levonorgestrel-exposed endometrium. Maximal MMP-9 immunoreactivity was evident at times when progesterone exposure was highest during the early and mid secretory phases, that is, around the time of anticipated implantation. MMP-9 may also have a role in menstruation with its expression maintained in the late secretory phase in association with progesterone withdrawal. Regulation of MMP-9 is clearly complex and it is likely to involve progesterone either directly or indirectly via other local mediators. High quantities of MMP-9 immunoreactivity were present in endometrium exposed to intrauterine progestagen delivered by the LNG-IUS, and MMP-9 may have a role in the aetiology of breakthough bleeding associated with the use of this intrauterine contraceptive system.

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# Administration of an antiprogesterone up-regulates estrogen receptors in the endometrium of women using Norplant™: a pilot study

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**Objective:** To determine the effect of a single dose of mifepristone (200 mg) on endometrial estrogen and progesterone receptors in Norplant™ users.

**Design:** A prospective single-blind placebo-controlled pilot study.

**Setting:** Women were recruited from a large family planning clinic and were studied either at the clinic or in a clinical research unit attached to a teaching hospital gynecology department.

**Patient(s):** Eight women using Norplant™ and experiencing vaginal bleeding more often than once every 24 days. All completed the study.

**Intervention(s):** Endometrial biopsies were taken after treatment with both placebo and 200 mg of mifepristone, both given at the start of a bleeding episode.

**Main Outcome Measure(s):** Expression of endometrial progesterone (PR) and estrogen (ER) receptors, ovulation, and vaginal bleeding.

**Result(s):** Mifepristone administration was associated with down-regulation of PR receptor subtype B and up-regulation of ER. Women treated with mifepristone showed a tendency to increased ovulation rates and reduced vaginal bleeding.

**Conclusion(s):** The effect of mifepristone on endometrial steroid receptors was consistent with functional inhibition of progesterone. The findings warrant further investigation of this regimen as a strategy to reduce frequent bleeding. (Fertil Steril® 2002;77:366–72. ©2002 by American Society for Reproductive Medicine.)

**Key Words:** Norplant™, mifepristone, bleeding, endometrium, contraception

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Irregular or breakthrough bleeding is perhaps the most frequent side effect of oral contraceptives (1); in some parts of the world, it is the commonest reason for discontinuation (2). Irregular bleeding is particularly associated with low-dose progestogen-only contraception (pills, implants, and progestogen-releasing intrauterine systems), which in most women do not completely inhibit endogenous ovarian activity. In a recent review of first-year continuation rates of Norplant™ contraceptive implants in the United Kingdom (3), over 50% of women who had the implants removed cited menstrual change as the reason. By 18 months after insertion, 20% of women attending a large family planning clinic in Scotland (4) had stopped using Norplant™, with 43% of them attributing discontinuation to irregular bleeding.

The mechanisms responsible for irregular bleeding are not well understood. The occurrence of erratic bleeding episodes does not clearly correlate with fluctuations in circulating concentrations of endogenous or exogenous steroids, nor with any particular pattern of endometrial histology. It is thought that breakthrough bleeding is probably related to molecular changes in the endometrium that disrupt vascular growth, function, and repair and disturb hemostatic mechanisms (5). Estrogen receptors have now been clearly demonstrated in the endothelium of the endometrial vasculature (6), and thus these changes may be mediated by

a direct or indirect effect of steroids on the vasculature acting via cytokines or chemokines (7).

Whatever the cause of breakthrough bleeding, it is well recognized that the addition of ethinyl estradiol to a progestogen-only contraceptive regimen reliably improves bleeding patterns (8, 9). More recently it has been demonstrated that the addition of an antiprogesterone to progestogen-only contraception reduces the incidence of unscheduled bleeding in monkeys (10), and we have shown that once a month administration of mifepristone improves bleeding patterns in Chinese women using the levonorgestrel-releasing sino-implant (11). The mechanism for this effect of both estrogen and mifepristone is unknown. In the normal cycle, after menstruation, a period of unopposed estrogen stimulation (during the follicular phase) appears to be necessary for the regeneration of endometrial progesterone receptors. Although the endometrium of women using Norplant™ has been shown to have an increased concentration of progesterone receptors (PR) (12, 13), exposure to progestogens can lead to refractoriness to the steroid (see 14 for review). It is possible that both add-back estrogen, acting directly on the endometrium, and antiprogesterone, through a direct effect on steroid receptors allowing the regeneration of functional PR, mimic this physiological process.

In an attempt to determine whether the addition of an antiprogesterone to a progestogen-only regimen of contraception might alter the expression of endometrial steroid receptors, we undertook a small pilot study of women experiencing troublesome bleeding while using the contraceptive implant Norplant™.

None of the authors has any vested interest of a commercial nature relevant to this study.

## PATIENTS AND METHODS

Eight women who had been using Norplant™ for at least 4 months and who were experiencing vaginal bleeding more than once every 24 days were recruited to the study from a large family planning clinic in Edinburgh. All eight women took both placebo and mifepristone treatment, and all completed the study. None complained of any side effects associated with either treatment. Women kept a daily diary of menstrual bleeding and spotting throughout the study.

Ovarian activity was monitored for 8 weeks by measuring estrone and pregnanediol/creatinine ratios in early morning specimens of urine collected three times every week. Samples from individual women were run in a single batch. Urinary estrone-3-glucuronide was measured using a specific radioimmunoassay and pregnanediol-3-glucuronide using an enzyme-linked immunosorbent assay (ELISA) (for full details see 15). A pregnanediol/creatinine ratio of 0.5 or more was taken as an indication of ovulation. On the third day after the onset of the first bleeding episode to occur after 8 weeks of baseline monitoring, a single placebo tablet (vitamin C, 50 mg) was given and urine collection was increased to daily (Fig. 1). In a similar manner, 200 mg of mifepristone was taken on day 3 of the first bleeding episode to occur at least 3 weeks after placebo treatment. Daily urine collection continued until 4 weeks after the administration of mifepristone. Participants were blinded to the treatments.

Between 3 and 5 days after administration of both placebo and mifepristone an endometrial biopsy was taken using a Pipelle endometrial sampler. On the day of the biopsy a single venous blood sample (10 mL) was taken for the measurement of estradiol and progesterone by RIA using methods that have previously been published from our center (16). A sample of cervical mucus was also collected using a tuberculin syringe (15). Cervical mucus score was assessed using the criteria established by the World Health Organization (17) wherein scores of 0 to 3 were given for mucus volume, consistency, ferning, spinnbarkeit, and cellularity (total score possible = 15).

All endometrial tissue samples were fixed overnight in 10% neutral buffered formalin at 4°C, rinsed, and stored in 70% ethanol and thereafter routinely wax embedded. Sections 5 $\mu$m thick were cut for routine histopathology (hematoxylin and eosin staining) and immunolocalization of progesterone receptor (subtypes A and B), progesterone receptor subtype B, and estrogen receptor.

Local ethics committee approval was obtained for the study and all participants gave written, informed consent.

Differences in bleeding patterns were analyzed using the Wilcoxon signed rank test and by paired $t$ test.

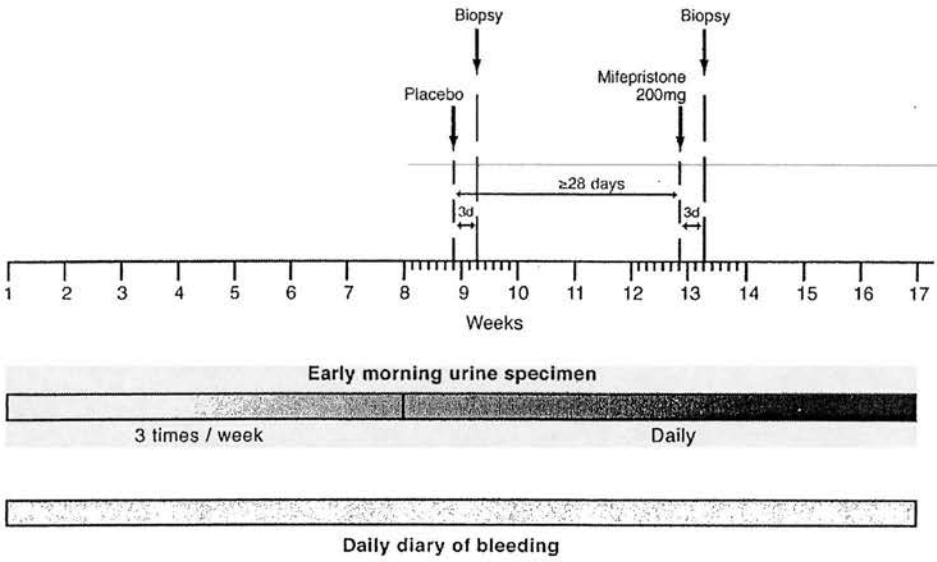
### Immunohistochemical Procedures

Localization of progesterone receptors was undertaken with the use of two antibodies, a rabbit polyclonal antibody against $PR_B$ subtype, and a monoclonal antibody that detects both A and B subtypes. It is not possible to raise a specific subtype antibody against the A form of the receptor. Hence, we refer to $PR_{A+B}$ as the receptor detected by the antibody that recognizes both subtypes of the PR, and $PR_B$ as the receptor detected by antibody specific to the B form of the receptor. Furthermore, we assume $PR_A$ is the subtype responsible for positive immunostaining when the B subtype cannot be detected. (For full details of the immunohistochemical protocols used in our study, see 18, 19).

Briefly, paraffin-embedded tissue sections were treated with primary antibodies raised against the A and B subtype of the progesterone receptor (1:40 Novocastra Laboratories, Newcastle, United Kingdom), the B form of the progesterone receptor (1:200 "in house" rabbit anti-human antibody [18]), and the estrogen receptor (1 in 25 ER1D5, DAKO Laboratories, High Wycombe, United Kingdom). An antigen-retrieval step (tissue sections microwaved in citrate buffer, pH 6.0 [18]) was necessary for localization of epitope representing the A and B form of the progesterone receptor and the estrogen receptor. Standard immunohistochemical

**FIGURE 1**

Study design.




*Glasier. RU486 and Norplant™treated endometrium. Fertil Steril 2002.*

detection methods were employed (avidin-biotin-peroxidase: Vectastain, PK-4002, DAB kit, SK-4100, Vector Laboratories, Peterborough, United Kingdom). Negative controls were included by replacing the primary antibody with nonimmune serum of equivalent concentration.

### Scoring of Immunohistochemical Staining and Statistical Analysis

Immunostaining intensity and distribution of epitopes in all tissue sections were assessed semiquantitatively, on a four-point scale where 0 = no staining, 1 = mild staining, 2 = moderate staining, and 3 = intense staining. Scoring was performed "blind" by a single observer. As we reported elsewhere, in endometrial tissue sections, a high correlation (0.963) of immunostaining was measured objectively by computerized image analysis and by subjective semiquantitative scoring of immunoreactivity (18). These published data support the subsequent statistical analyses performed on semiquantitative scores of sex steroid immunostaining. As the data were noncontinuous, analysis employed a Mann-Whitney test.

## RESULTS

The characteristics of the women and their responses to treatment with mifepristone and placebo are shown in Table 1. The amount of tissue from one woman following placebo

**TABLE 1**

Menstrual bleeding pattern reported with mifepristone and placebo.

| | Bleeding/spotting days | | Dry days | | |
|---|---|---|---|---|---|
| Treatment | Mean | Range | Mean | Range | Women ovulated |
| After placebo | 6 | 0–21 | 14 | 8–39 | 1 |
| After mifepristone | 4 | 0–6 | 17 | 8–>25 | 3 |

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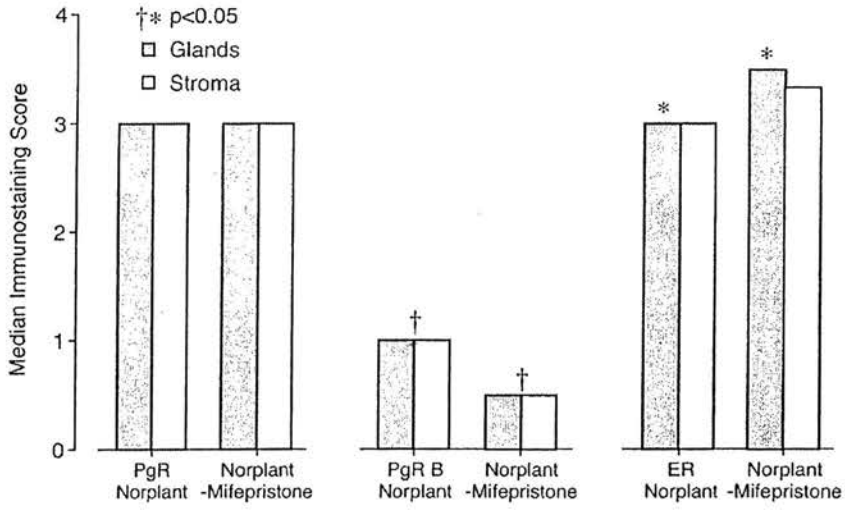
FIGURE 2

Semiquantitative immunostaining scores (median value) of progesterone receptor (PgR) (A and B isoforms), progesterone receptor B ($PgR_B$) isoform, and estrogen receptor (ER) in endometrium after placebo and after mifepristone. 0 = no immunostaining; 3 = intense immunostaining.




*Glasier. RU486 and Norplant™treated endometrium. Fertil Steril 2002.*

treatment, and from the same woman and one other following mifepristone administration was inadequate for analysis; thus, seven biopsies were available after placebo treatment and six after mifepristone.

## Steroid Receptor Immunostaining

The response of receptor expression to the administration of mifepristone in endometrium exposed to Norplant™ is shown in Figure 2. Levonorgestrel-exposed endometrium displayed intense immunostaining for PR subtype $_{A+B}$ in both stromal and glandular cells. Administration of mifepristone was not associated with any change in this pattern. Endometrium exposed to levonorgestrel displayed a lower level of immunostaining for PR subtype B than for $PR_{A+B}$ in both glands and stroma; $PR_B$ expression was significantly further reduced following mifepristone ($P<.05$) (Fig. 3).

Estrogen receptor immunoreactivity was intense in both glandular and stromal components of the Norplant™ (levonorgestrel-treated) endometrium. Mifepristone administration was followed by a significant increase in ER immunoreactivity in glandular cells ($P<.05$).

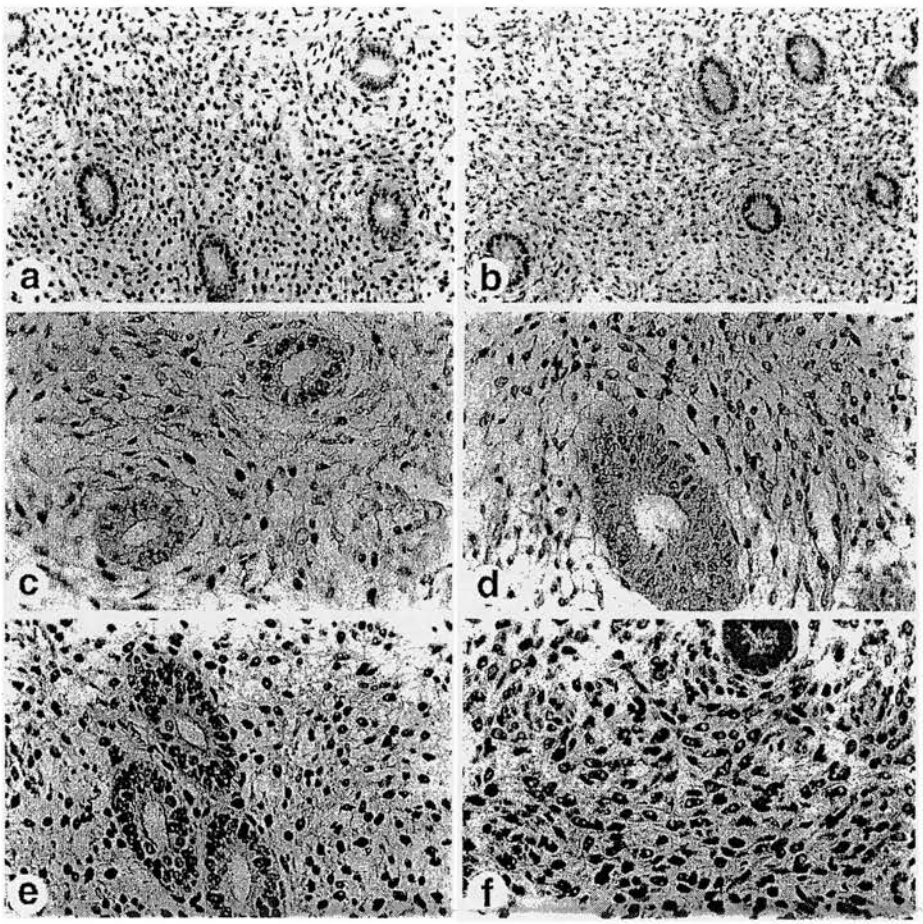
## Bleeding Patterns, Ovarian Activity, and Cervical Mucus Characteristics

Both placebo and mifepristone were administered on the third day of an episode of vaginal bleeding. The mean number of days during which women continued to experience bleeding or spotting after treatment was slightly less (4 days, range: 0 to 6) following mifepristone than after placebo treatment (6 days, range: 0 to 21). The mean number of days when no bleeding or spotting occurred (dry days) following the end of the "treatment episode" until the onset of the next episode of bleeding or spotting was slightly longer following administration of mifepristone (17 days, range: 8 to >25) than after placebo (14 days, range: 8 to 39). Neither of these observations reached the level of statistical significance. Because the study ended 4 weeks after mifepristone treatment, it was not possible to determine the total number of dry days in every woman; two had experienced no further bleeding by the time the study ended.

Following mifepristone administration (see Table 1), three women ovulated and two others had an increase in pregnanediol/creatinine ratio, which did not reach a value consistent with normal ovulation (>0.5). In comparison, only two women showed signs of ovulation during the

**FIGURE 3**

Strong positive nuclear progesterone receptor (PgR) immunostaining (brown) was observed in glands and stroma of endometrium treated with (a) Norplant™ and (b) mifepristone-Norplant™. (c), Lower positive progesterone receptor B ($PgR_B$) immunostaining was apparent in glands and stroma of Norplant™treated endometrium. (d), Positive progesterone receptor B ($PgR_B$) immunostaining was present in few cells of glands and stroma of mifepristone-Norplant™treated endometrium. (e), Strong estrogen receptor (ER) immunostaining was observed in glands and stroma of Norplant™treated endometrium. (f), Intense estrogen receptor (ER) immunostaining was observed in glands and stroma of endometrium treated with mifepristone-Norplant™.




*Glasier. RU486 and Norplant™treated endometrium. Fertil Steril 2002.*

8-week pretreatment period and only one woman ovulated in the 4 weeks following placebo. There were no clear differences identifiable in endometrial steroid receptor immunostaining between the women who did or did not ovulate. In no woman did ovulation occur before the time of the biopsy.

No cervical mucus was detectable in any of the women on the day of placebo treatment. On the day of mifepristone administration, cervical mucus was detectable in only one woman, in whom the total score was 6.

There were no pregnancies during the course of the study.

## DISCUSSION

The findings of this pilot study lend support to our hypothesis that the administration of an antiprogesterone might functionally inhibit the actions of levonorgestrel, despite its continued delivery from Norplant™ implants. A possible mechanism for this is as follows. The predominant steroid receptor pattern in levonorgestrel-exposed endometrium is characterized by maximal expression of subtype A with a reduction in expression of both PR subtype B and estrogen receptors. This is a similar pattern to that observed during the luteal phase of the normal cycle and one where it is associated with endometrial breakdown and vaginal bleeding. Thus, the chronic exposure to low-dose levonorgestrel is associated with an endometrium constantly liable to degenerate. Mifepristone administration causes further reduction of the expression of $PR_B$ receptors, amplifying the lack of progesterone action and inducing menstruation. The simultaneous up-regulation of estrogen receptors induces the factors responsible for endometrial proliferation, causing cessation of bleeding and a period of bleed-free days until endometrial shedding recurs as the background pattern of endometrial receptor status associated with Norplant™ (high $PR_A$, low $PR_B$, and low ER) is restored.

The actual mechanism by which the steroids act on the endometrial vasculature is unknown. However, increased immunostaining for matrix metalloproteinases (MMPs), which are involved with tissue breakdown, has been described in the endometrium of Norplant™ users (20) and these enzymes have been implicated in endometrial breakdown at the onset of menstruation in the normal cycle (7).

Like other investigators (12, 13), we have shown in this study that PR concentrations are high in both the glandular and stromal cells of the endometrium of women exposed to levonorgestrel delivered by Norplant™. We have also demonstrated, for the first time, the presence of PR subtype B receptors in endometrium exposed to Norplant™. It is clear from Figure 3 that $PR_B$ immunoreactivity in glandular and stromal cells is much lower than the immunoreactivity for $PR_{A+B}$, which we infer to represent PR subtype A (18). Mifepristone administration resulted in further depression of the B subtype receptor. The simultaneous up-regulation of estrogen receptors as a result of mifepristone administration may be an indication of the functional withdrawal of progesterone and its effects on the endometrium.

There are no data on endometrial vessel changes in women using Norplant™, who have been exposed to an antigestogen. We and others have reported that the $PR_A$ isoform is likely to be the dominant isoform in the secretory phase of the cycle (18, 21). Moreover, $PR_A$ is the dominant form in differentiating stromal cells in vitro. The abundance of $PR_A$ declines in vitro during the decidualization process (22). A decline in PR levels, either $PR_A$ or $PR_B$, will be of functional importance as there is differential gene activation. Moreover, $PR_A$ may act as a repressor of $PR_B$ function, and the expression ratios of the two subtypes will determine the response to progesterone/progestogen (21, 23).

Mifepristone may also have an effect on the hypothalamus, stimulating positive feedback by blocking the inhibitory action of progesterone and inducing ovulation (16), an action which, independent of any direct effect on the endometrium, would be sufficient to improve bleeding patterns. Certainly there was a suggestion in our study that ovulation was more likely to occur during the 4 weeks after mifepristone administration than during the weeks before and after placebo.

Cheng et al. (11) demonstrated an improvement in bleeding patterns when mifepristone was administered to women experiencing bleeding dysfunction while using the levonorgestrel contraceptive implant. In that study ovarian activity was not monitored, so we do not know whether the improvement was due to induction of regular ovulation or to some other direct effect on the endometrium as described above.

Bleeding patterns tend to improve with the duration of use of Norplant™ (11, 24), probably because as circulating concentrations of levonorgestrel fall ovulation becomes more frequent—about one-third of women ovulate regularly. The altered endometrial vessel morphology described by Hickey et al. (25) coincides with the time when bleeding problems are most common. In our study, the duration of Norplant™ use varied between 4 and 24 months, but only two women showed evidence of ovulation during the pretreatment period (8 weeks) and all were experiencing frequent bleeding episodes. It is possible that mifepristone may have a different effect depending on the duration of Norplant™ use, but the sample size in this small pilot study was insufficient to assess this.

It is possible then that the regular administration of an antiprogesterone—for example, once each month—might be a useful strategy for reducing the side effects of low-dose progestogen-only contraceptives, thereby increasing both acceptability and continuation rates.

Norplant™ is a highly effective method of contraception that has three mechanisms of action. It inhibits ovulation, prevents normal sperm transport through the female genital tract (particularly through the cervix), and is associated with endometrial atrophy (24). If mifepristone administration increases the number of ovulatory cycles, it might reduce the contraceptive efficacy of Norplant™ at the expense of inducing more tolerable bleeding patterns. Ovulation is infrequent during the first 2 years of Norplant™, but it increases with time as discussed earlier. However, the cumulative pregnancy rate at the end of 5 years is only 1.1%, and thus it would seem unlikely that an increase in the frequency of ovulation following mifepristone would significantly increase the failure rate of Norplant™.

In the clinical trial of once a month mifepristone admin-

istration (11), there were no pregnancies during 300 woman-months of use. Contraceptive efficacy could also be reduced if antiprogesterone improved the quality of cervical mucus. No woman showed any evidence of having fertile mucus at the time when placebo and mifepristone were given. It is however possible that the functional inhibition of progesterone by mifepristone might induce fertile mucus, which we failed to detect as we did not collect samples within days of mifepristone administration.

Although ours was only a small pilot study, our observations suggest that further investigation of the effects of an antiprogesterone on the endometrium, and on vaginal bleeding patterns, in women using long-acting low-dose progestogen-only contraceptives would be worthy of future study.

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# Once a month administration of mifepristone improves bleeding patterns in women using subdermal contraceptive implants releasing levonorgestrel

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**It has been suggested that the administration of an anti-progesterone might improve bleeding patterns in women with irregular bleeding while using low-dose progestin-only contraception. We report the findings of a double-blind, randomized, placebo-controlled trial of mifepristone 50 mg taken once every 4 weeks in 100 Chinese women (50 subjects and 50 controls) complaining of frequent and irregular bleeding while using a levonorgestrel-releasing subdermal contraceptive implant. In all women, regardless of treatment, the frequency of bleeding decreased significantly over 360 days of observation. Women recorded significantly shorter episodes of bleeding ($P < 0.0002$) during mifepristone treatment than during the 90 days before treatment started. In contrast, the duration of bleeding episodes fell more gradually in placebo-treated controls. Women using mifepristone were more likely to find treatment acceptable than women receiving a placebo tablet ($P < 0.01$). Despite concern that anti-progestogenic effects may jeopardize contraception, there were no pregnancies. This approach may offer a useful strategy to improve continuation rates by alleviating unwanted side-effects until bleeding patterns improve spontaneously with time.**

*Key words:* bleeding/contraception/implants/mifepristone/progestin-only

## Introduction

Progestin-only contraceptive implants offer highly effective contraception that is long-acting and does not require compliance for effectiveness. The major side-effect is an irregular pattern of uterine bleeding (Fraser *et al.*, 1998). At the end of 5 years, some 25% of Norplant users will have requested removal of the implants because of a bleeding problem (Sivin *et al.*, 1998). In the People's Republic of China, levonorgestrel-releasing implants account for only a very small amount of contraceptive use, in Shanghai <1% of women use the Sino-implant (Shanghai Dahua Pharmaceutical Plant, Shanghai, China). In a multicentre study (undertaken in China) of two types of levonorgestrel releasing implants, menstrual disturbance accounted for 90% of the reported side-effects and led to a discontinuation rate of 11% at the end of 1 year (Fang *et al.*, 1998).

Although the mechanisms underlying menstrual disturbance are not completely understood (Fraser *et al.*, 1997; Hickey *et al.*, 1999a,b) a variety of approaches have been tested to reduce irregular bleeding in association with progestin-only contraception and thereby to improve continuation rates (Fraser, 1983).

It has been demonstrated that the addition of an antiprogesterone to progestin-only contraception reduces the incidence of unscheduled bleeding in monkeys (Williams *et al.*, 1997). In a small pilot study among women using Norplant®, we have demonstrated that a single dose of mifepristone 200 mg induces changes in endometrial progesterone and oestrogen receptors which are consistent with the functional inhibition of progesterone. There was a suggestion that anti-progesterone treatment might improve bleeding patterns, either by a direct effect on the endometrium or by inducing ovulation (Wang *et al.*, 1997). In an attempt to see whether the monthly administration of a single dose of anti-progesterone might confer a clinically significant improvement in bleeding patterns, we undertook a double-blind randomized trial of once a month administration of mifepristone to women using the Chinese levonorgestrel-releasing implant (Sino-implant).

None of the authors has any vested interests of a commercial nature relevant to this study.

## Materials and methods

One hundred women aged 18–40 years were recruited from three family planning clinics on the outskirts of Shanghai. All had been using, for at least 3 months (range 3–43, median 15 months), a contraceptive implant (Sino-implant; Shanghai Dahua Pharmaceutical Plant) comprising two rods, each containing 75 mg levonorgestrel, delivering a total dose of 30 μg/day for 3 years. All women were attending the clinic complaining of frequent vaginal bleeding, defined as a bleeding episode occurring more often than once every 24 days. None was receiving any medication and all were fit and well with no history of any gynaecological disease. Local ethical committee approval was obtained for the study and informed consent was given by all participants.

Women were randomized (50 in each group), using random number tables, in blocks of eight attending each clinic, to receive either 50 mg mifespristone (two tablets of 25 mg each) or two placebo tablets (both placebo and mifepristone were provided by the Shanghai Hualian Pharmaceutical Co. Ltd, Shanghai, PR China). Treatment was administered in a double-blind manner.

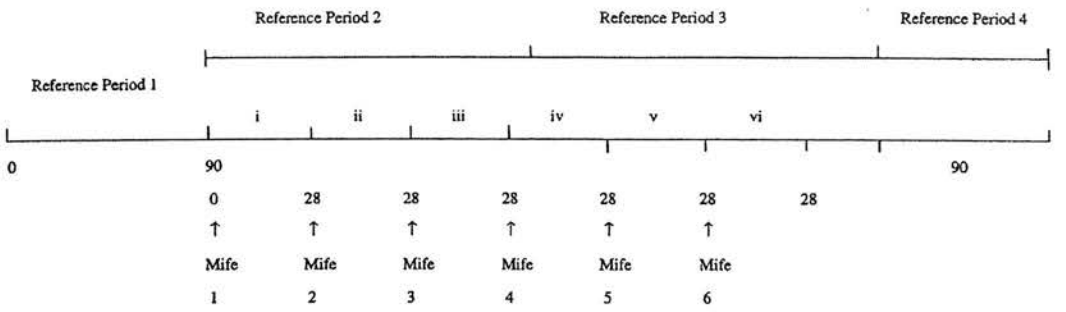


**Figure 1.** Study design and reference periods for analysis of bleeding patterns. Mife = mifepristone 50 mg or placebo.

All women were instructed to keep a daily diary of bleeding and spotting. Spotting was defined as vaginal blood loss not requiring sanitary protection. After being enrolled in the study, a record of bleeding was kept for 90 days prior to starting treatment. After completion of 90 days of record-keeping, women were instructed to attend the family planning clinic for the first treatment on the third day after the start of a bleeding/spotting episode. After the first treatment women were given a date to return to the clinic once every 28 days for 5 months (a total of six treatments in all). Treatment was always given at the family planning clinic, where pill taking was observed by a doctor after urinary β-human chorionic gonadotrophin (HCG) had been measured to exclude pregnancy. At this visit the bleeding diary was checked. Bleeding diaries were continued for a further 90 days after completion of the last cycle of treatment.

Urinary HCG was measured using a kit (Surestep™ HCG; Applied Biotech Inc., San Diego, CA, USA), the lower level of sensitivity of which was 25 IU/l.

### *Statistical analysis*

Since we had no meaningful data on which to base power calculations the sample size was chosen to give sufficient power to detect as significant a mean difference of 0.6 standard deviations. Menstrual diaries were analysed using the MDS Menstrual Diary Analysis Programme (World Health Organization, Special Program of Research, Development and Research Training in Human Reproduction, Statistics and Data Processing Unit, Version 3.0. 1993) (WHO, 1996).

Bleeding patterns were analysed in blocks of 90 days (reference periods) (Figure 1). For each reference period the number of days of bleeding and spotting, the number of episodes of bleeding and spotting; the mean duration of spotting and bleeding episodes and the number of 'dry days' (free of bleeding and spotting) were calculated. Thus reference period 1 includes 90 days before the first treatment (mifepristone or placebo). Reference periods 2 and 3 cover a total of 180 days from the first treatment and together include 6 treatment months and the first 12 days of month 7. Reference period 4 started 39 days after the last treatment and ended 90 days later (Figure 1).

In the final analysis, bleeding and spotting days were combined and the data analysed using the Mann–Whitney *U*-test.

## Results

There were no differences in age (29.5 years for subjects, 30 years for controls) or parity (2.6 for each group) between subjects and controls nor in the mean duration of implant use (15.8 ± 2 months for subjects and 16.5 ± 2 months for controls). All women completed the study and there were no pregnancies.

**Table I.** Degree of satisfaction with treatment [numbers (and percentages) of women]

| | *n* | Satisfied | Neutral | Dissatisfied |
|---|---|---|---|---|
| Subjects | 48 | 18 (37) | 21 (44) | 9 (19) |
| Controls | 49 | 9 (18) | 20 (41) | 20 (41) |

The effect of treatment on bleeding patterns is shown in Figure 2. There were no statistically significant differences between subjects and controls in any of the parameters assessed during the 90 day period before treatment was started. Women in both groups tended to show a similar decrease in the number of bleeding days (and therefore an increase in the number of dry days) with time (Figure 2A). Women treated with mifepristone bled for a mean of 48 ± 15 days (range 21–88) during the first 90 days, falling to 29 days in reference period 2 ($P < 0.0002$) with a further decrease to 23 days during reference period 3. Women treated with placebo recorded a mean of 51 ± 15 days (range 27–89) of bleeding in reference period 1, falling to 33 days ($P < 0.0002$) during reference period 2. By reference period 4 (after treatment), there were no significant differences between subjects and controls in any of the bleeding parameters measured. The mean number of bleeding and spotting episodes also fell with time (Figure 2B), with no significant difference between women treated with mifepristone and controls. The most marked difference between the two groups was in the average duration of bleeding episodes (Figure 2B) which, among the subjects, fell from a mean of 14 days before treatment to 6.5 days after the first 90 days of treatment ($P < 0.00001$). Among controls, the mean duration of bleeding episodes also fell significantly with time from 15 days during the 90 days before treatment to 11.1 days at the end of the first 90 days of treatment ($P = 0.0003$) and 8.2 days after the completion of all six treatment cycles. The mean duration of bleeding episodes almost halved for both groups of women when the number during the pre-treatment period was compared with that post-treatment, regardless of whether they had been treated with placebo or mifepristone.

Forty-eight subjects and 49 controls completed the post-

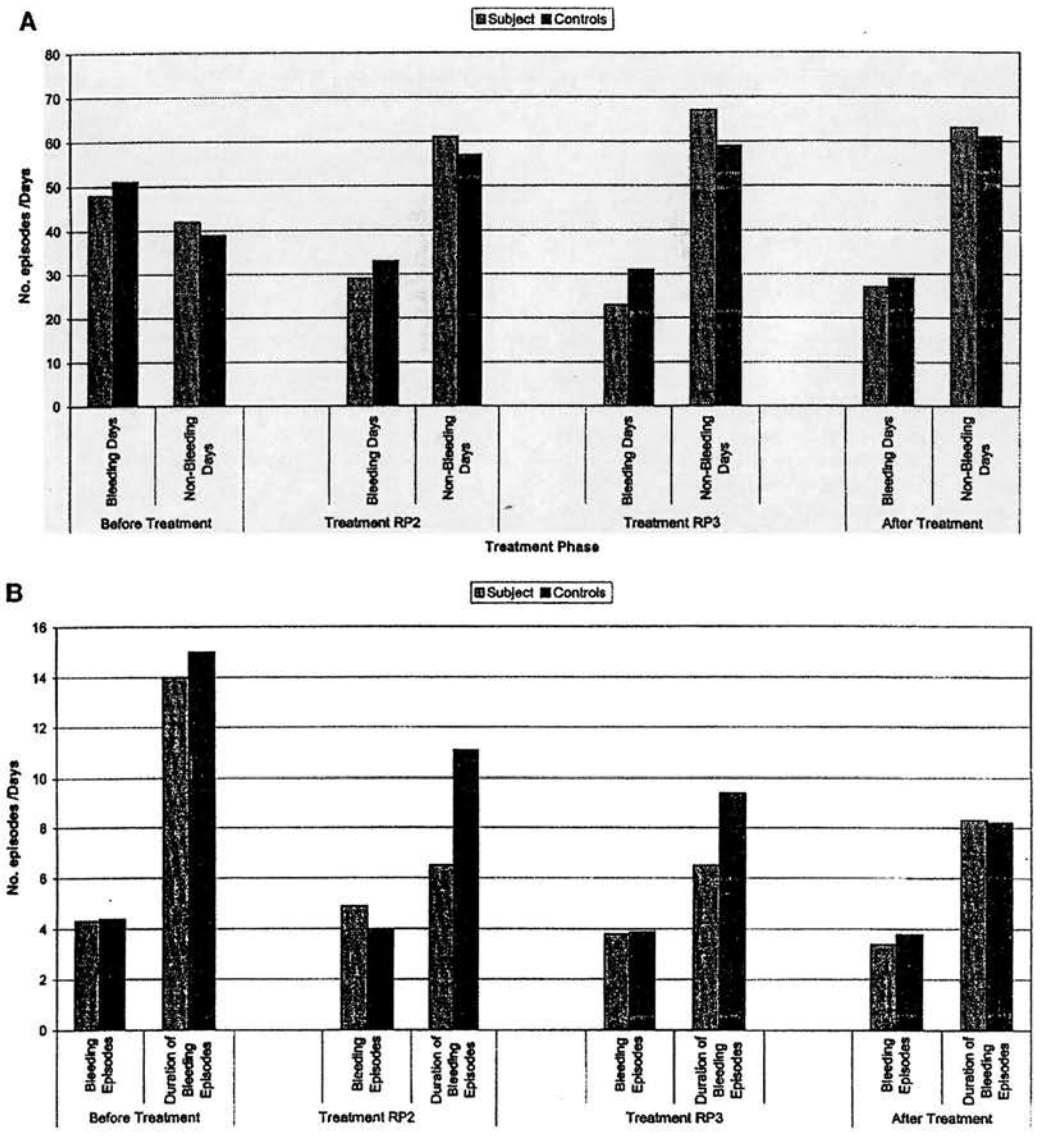


Figure 2. Mean number of bleeding and dry days (A) and number and duration of bleeding episodes (B) among mifepristone-treated women and controls over the four reference periods (RP).

treatment satisfaction questionnaire. Women treated with mifepristone were more likely to rate their treatment as satisfactory than those who received placebo ($P < 0.01$, Table I).

## Discussion

In all women using the Sino-implant, bleeding patterns improved during the 360 days of follow-up. The number of bleeding days decreased (and inevitably therefore the number of dry days increased) and both the number and duration of bleeding episodes was reduced to a similar extent regardless of treatment. This tendency for bleeding patterns to improve has been observed with Norplant (Shoupe *et al.*, 1991) and has been attributed to an increase in the frequency of ovulation as concentrations of levonorgestrel delivered by the implant gradually fall. We analysed the number of bleeding and spotting days and number of bleeding episodes (among both subjects and controls and both groups combined), comparing women who had been using the implants for durations of less than the median with those who had been using them for longer than the median duration for the group. While there did appear

**Table II.** Mean number of bleeding and spotting days and mean number of bleeding episodes per 90 day reference period among women with shorter (less than median) or longer (longer than median) durations of implant use

| Patient | Duration of implant use | *n* | Mean number of bleeding/spotting days | Mean number of bleeding episodes |
|---|---|---|---|---|
| Subjects | More than median | 24* | 44.0 ± 16 | 4.1 ± 1 |
| (median 13.5 months) | Less than or equal to median | 24* | 51.2 ± 14 | 4.3 ± 1 |
| Controls | More than median | 25 | 46.2 ± 13 | 4.3 ± 1 |
| (median 15 months) | Less than or equal to median | 25 | 54.9 ± 15 | 4.4 ± 1 |
| All patients | More than median | 45 | 45.6 ± 14 | 4.3 ± 1 |
| (median 14 months) | Less than or equal to median | 53 | 52.1 ± 15 | 4.3 ± 1 |

*Data inadequate for one subject in each group.

to be a slight improvement (Table II), the differences were not statistically significant, in contrast to the differences seen in response to mifepristone administration. The incidence of side-effects also has been reported to decrease with time among women using the Sino-implant (Fang *et al.*, 1998), although whether this is due to an increase in ovulatory cycles is not known.

The only significant effect of mifepristone treatment was on the average duration of bleeding episodes, which more than halved in length during mifepristone-treated cycles but changed much more gradually in women receiving placebo tablets. The duration of bleeding episodes during mifepristone resembled a 'normal' menstrual period. Since ovarian activity was not monitored during the study, it is not possible to determine whether induction of ovulation was the cause of the improvement in bleeding patterns. Further studies, with monitoring of ovarian activity, need to be undertaken.

While these results may seem somewhat disappointing, the women clearly found mifepristone to be of benefit. It hardly needs scientific methodology to confirm that a bleeding episode of shorter duration has to be more acceptable than one that continues for days on end.

Levonorgestrel contraceptive implants act mainly by changing the quality of cervical mucus and inhibiting normal sperm penetration (Croxatto *et al.*, 1987). Abnormal endometrial development will prevent implantation, should fertilization occur. Any intervention designed to improve bleeding patterns which 'inhibits' the action of the progestogen might theoretically jeopardize contraception. Reassuringly, no woman conceived during 300 'cycles' of use of mifepristone in combination with the Sino-implant. In the event that administration of an anti-progesterone might reverse the contraceptive effects of the progestogen, mifepristone itself at a dose of 50 mg has both contraceptive and abortifacient effects and the risk of pregnancy may in fact be reduced still further.

The results of this study suggest that the once a month administration of mifepristone may be an effective and acceptable way to ameliorate bleeding irregularities and 'tide women over' until bleeding patterns improve with time as a consequence of an increasing frequency of ovulatory cycles. It is possible to achieve a similar effect with the combined oral contraceptive pill (Diaz *et al.*, 1990), but most women find the idea of using two hormonal contraceptives simultaneously hard to understand and many have chosen a long-acting implant because they do not like – or cannot remember – to take a pill every day. Further, and more detailed, studies of the mechanism of action of this regimen are warranted.

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# Clinical review

*Science, medicine, and the future*

## Contraception

David T Baird, Anna F Glasier

The prevalence of contraceptive use is increasing worldwide, and in many countries over 75% of couples use effective methods.[1] However, existing methods of contraception are not perfect, and their acceptability is limited by side effects and inconvenience. Even in developed countries where contraception is freely available, many unplanned pregnancies occur. There is thus a real need for new methods of contraception to be developed that are more effective, easier to use, and safer than existing methods. This article discusses current research into new forms of contraception and predicts what methods are likely to be used in the future.

### Social influences

Demographic forces, prevalence of disease, and social and cultural factors influence not only the use of contraceptives but also the development of new methods. The age of onset of sexual activity is falling, while childbearing is being delayed or, in many developed countries, forgone altogether. There is pressure from the public for the use of more "natural products," which are perceived to be safer, but at the same time demand that contraceptives have almost perfect efficacy.

Those concerned with the development of new drugs and devices take efficacy as read and are now seeking positive health benefits—methods that prevent not only pregnancy but also sexually transmitted disease and, in the long term, common diseases such as breast cancer. Heterosexual intercourse is now the main route of transmission of HIV. While barrier methods such as condoms reduce the risk of transmission, there is a pressing need for additional and complementary methods of protection in the form of topical virucidal agents, which ideally would also be spermicidal.

### Hormonal contraception for women

Methods involving steroid hormones have dominated new developments in contraception, and in the past 40 years more than 200 million women worldwide have taken "the pill."[2] Recent data confirm its excellent safety profile, and in many respects the pill will be hard to beat. In the past 15 years new developments in contraception have come mainly from tinkering with hormonal methods—new delivery systems (implants and hormone releasing intrauterine devices), better progestogens, and lower doses of oestrogen.

**Predicted developments**

**Within five years**
- New delivery systems of conventional contraceptives, such as vaginal rings, transdermal patches, and gels
- Contraceptives that also protect against sexually transmitted disease

**Short term (<10 years)**
- "Once a month" pill that inhibits implantation
- Antiprogestogens used for oestrogen-free, daily pill for women
- Orally active, non-peptide antagonists of gonadotrophin releasing hormone for men and women

**Long term (>10 years)**
- Antagonists of follicle stimulating hormone receptor
- Arrest of spermatogenesis or sperm maturation
- Arrest of final maturation of oocyte, such as with phosphodiesterase inhibitors
- Inhibitors of follicle rupture

#### New delivery systems and selective receptor modulators

The early 21st century will probably witness the licensing of contraceptive vaginal rings, transdermal patches, and gels. In the longer term it seems likely that selective modulators of hormone receptors will replace currently available oestrogens and progestins in order to avoid their risks, particularly venous thrombosis, while also reducing the incidence of common diseases such as breast cancer. Study of the molecular structure of hormone receptors has revealed that each ligand induces an almost unique conformational change and, hence, has slightly different biological effects.[3] It is therefore likely that organ specific drugs, which produce the desired effect only on critical reproductive processes, will become available.

#### Antiprogestins

The most exciting development in the past 20 years has been the discovery of compounds that antagonise the action of progesterone. Progesterone is necessary for the establishment and maintenance of pregnancy. Key events—including ovulation, fertilisation, and

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implantation—depend on the secretion of progesterone by the ovary at the appropriate time. It is nearly 20 years since the discovery of the first antagonist of progesterone (mifepristone), which was shown to interrupt pregnancy. The political controversy surrounding the "abortion pill" has impeded research into other potential uses of these compounds, including contraception.

Some years ago we showed that a single dose of 600 mg mifepristone was highly effective as an emergency contraceptive after unprotected intercourse.[4] The compound both inhibits ovulation and prevents implantation, properties which suggest that it could be used as a regular form of contraception. A daily dose of 2-5 mg (less than a hundredth of the dose required to induce abortion) inhibits ovulation and prevents the formation of a secretory endometrium.[5] Oestrogen secretion by the ovary is maintained at the level of that found in the follicular phase of the menstrual cycle. Preliminary data suggest that most women are amenorrhoeic while taking the antiprogestin, which could be a considerable advantage compared with other forms of oestrogen-free contraceptives such as gestogen only pills.

Antigestogens might also be used for "once a month" pills. If they are given in the early luteal phase of the cycle the formation of a secretory endometrium is retarded without affecting the regular pattern of menstruation. In a pilot study of 21 women in Sweden who used this method as their sole means of contraception there was only one pregnancy in 153 menstrual cycles.[6] A major practical problem with this approach is the difficulty in detecting ovulation so that the pill can be taken at the correct time of the cycle. A once a month pill that prevented ovulation or implantation would be welcomed by many women from various countries and cultures.[7] In contrast, only a minority of women would be prepared to use a pill taken around the time of expected menses, when implantation of the embryo would already have occurred. In any case, current evidence suggests that mifepristone alone or in combination with misoprostol would result in too high an incidence of pregnancy to be useful as a regular method of inducing early menses.[8]

### Contragestion

It has also been proposed that mifepristone could be taken only if the menses was overdue ("contragestion"). An inducer of a missed menses acts by disrupting an implanted embryo and induces a very early abortion. A pilot study supported by the World Health Organisation reported very few ongoing pregnancies in women given a combination of 600 mg mifepristone and 1 mg gemeprost within 10 days of their expected menses.[9] Although this study showed "proof of concept," there are legal, political, and ethical issues that make it unlikely that this approach would receive widespread acceptance. Moreover, in the above study there was considerable variation in the timing of the onset of the next menses, which would make it difficult for women to decide whether to take the pill again in subsequent cycles. However, for those women who find it ethically acceptable, a pill that induced missed menses might be more attractive than a monthly pill to induce early menses, perhaps because it would be required only two or three times a year.

## Hormonal contraception for men

Evidence from different countries and cultures shows a growing demand for more effective and convenient methods of contraception for men.[10] A recent survey in Scotland, South Africa, Hong Kong, and China found that most men would consider using a "male pill." Although it has been known for nearly 50 years that azoospermia can be induced by the administration of large doses of testosterone, progress in the development of hormonal male contraception has been slow for several reasons. The supraphysiological dose of androgen required to induce azoospermia causes side effects, including prostate hypertrophy and unfavourable changes in plasma lipids, precluding wide scale use in otherwise healthy men.[11]

Current research therefore focuses on lower physiological doses of androgen in combination with gestogens (such as desogestrel and cyproterone acetate) or gonadotrophin releasing hormone antagonists.[12] Orally active non-peptide antagonists of gonadotrophin releasing hormone or a depot preparation could provide a practical method of suppressing gonadotrophins in combination with androgen replacement. However, there are presently no convenient, safe preparations of androgen for replacement therapy, although this is the subject of research by several pharmaceutical companies. Encouraging progress is being made in the development of new androgens (such as 7α-methyl nortestosterone (MENT)) that have potential health benefits and in new methods of long term delivery of steroids in implants (such as Implanon).[13] Development of a safe, acceptable treatment that is as effective as the combined oral contraceptive pill for women (Pearl index $< 1$ per 100 women years) is at least five years away.

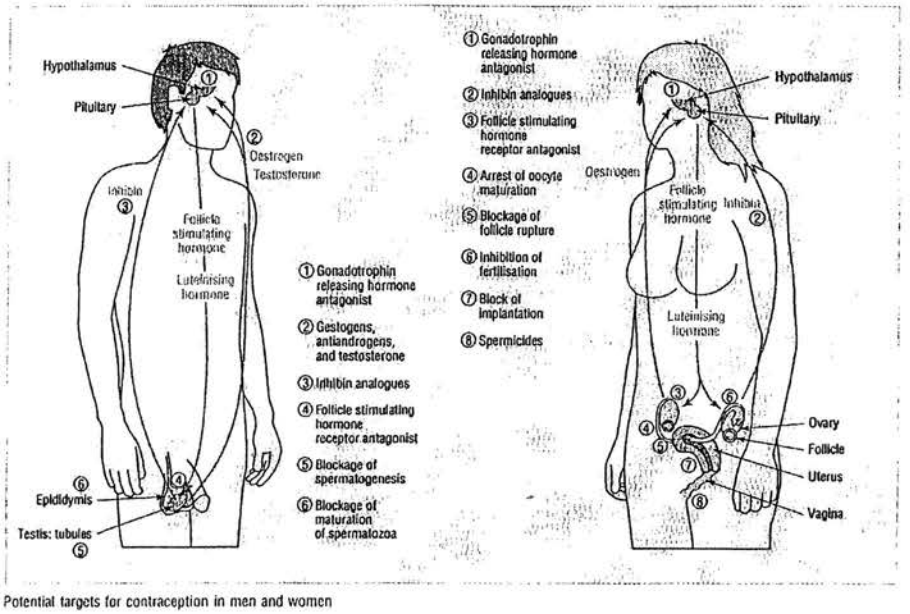
## Beyond 2010

In the long term there are several potential approaches for contraception in men and women (see figure).[14]

### Meiotic arrest

In both sexes the formation of gametes (spermatogenesis and oogenesis) involves the process of meiosis, whereby the number of chromosomes in a diploid nucleus is halved to the haploid state by cell division. Meiosis occurs only in germ cells, and, hence, substances that interfere with meiotic division should be specific for the gonad. Specific genes are expressed at different stages of spermatogenesis, and antagonism of their products (such as activin) could lead to sterility.

In the female, meiosis is almost completed during fetal development, but the final stages of meiotic division are delayed into adulthood, until just before ovulation. If we knew the mechanism by which meiosis was arrested in the oocyte it might be possible to activate a similar mechanism to inhibit spermatogenesis in men. Arrest of meiosis in the oocyte involves at least one protein specific to germ cells (c-mos), which is also transcribed in the male during meiosis. A high concentration of cyclic AMP is apparently important in preventing final maturation of the oocyte, and specific inhibition of phosphodiesterase 3 (the enzyme that catalyses the breakdown of cyclic AMP) is contraceptive in rats, preventing the oocyte from acquiring developmental competence.




Potential targets for contraception in men and women

**Blockage of follicle stimulating hormone**

Blocking the follicle stimulating hormone receptor or inhibiting secretion of follicle stimulating hormone with analogues of inhibin will interfere with spermatogenesis, although whether sperm production can be maintained by testosterone alone in men, as it can in rodents, is not known. A minimum concentration of testosterone within the testis is probably required for spermatogenesis, so that inhibitors of androgen synthesis or action will be contraceptive. The key to successful use of these approaches is again specificity. It may be possible to use the follicle stimulating hormone receptor as a target to deliver another agent specifically to the testis.

Mutations of the follicle stimulating hormone receptor have been described in women who present with primary amenorrhoea due to lack of follicle development. Inhibitors of follicle stimulating hormone synthesis or action could prevent fertility but would require oestrogen replacement to prevent the consequences of hypo-oestrogenism. Arresting final maturation of the oocyte before ovulation or follicle rupture would be an attractive method of contraception that did not disrupt the endocrine events controlling the ovarian cycle.

**Preventing implantation**

Progesterone induces the transcription of various endometrial gene products involved in implantation—for example, leukaemic inhibitory factor, calcitonin, vitronectin, $\alpha_v\beta_3$ integrin, and $\alpha_4\beta_1$ integrin.[15,16] Specific antagonists of these products would be promising as new contraceptives because they should only act at the uterus.

The formation of new blood vessels (angiogenesis) is usually restricted in adults to repair of injury, but in the ovary and uterus there is extensive angiogenesis each month during the formation of the follicle, corpus luteum, and endometrium. A potent antagonist of vascular endothelial growth factor prevented pregnancy in mice without producing major systemic side effects in the long term.

**Immunisation**

Other likely targets for new contraceptives are proteins involved in fertilisation.[17,18] The sperm attaches to the egg through the interaction of specific antigens on the sperm surface with the zona pellucida proteins of the egg (such as ZP3). Immunisation of female monkeys with zona pellucida proteins prevents pregnancy, but unfortunately produces a form of autoimmune oophoritis with loss of oocytes and premature menopause. Unforeseen consequences resulting from autoimmunity are a potential hazard of antifertility vaccines. Immunisation of women against sperm antigens should avoid such problems, but research is still at the initial stages.[19]

Another possibility is disrupting the synthesis or delivery of proteins such as fertilin that are important for the function of sperm membrane, thus leading to incompetent spermatozoa. Interfering with the final maturation of the spermatozoa has the attraction that it would result in sperm that were incompetent to fertilise an egg without running the risk of producing genetically mutated germ cells. However, concerns have been raised about the potential misuse of contraceptive vaccines, particularly if they are not fully reversible.

Because of these political concerns and doubt about long term consequences of immunisation, there is little commercial enthusiasm for further development of this approach in spite of the scientific potential.

## Conclusions

Compared with many drugs, the product development of a new contraceptive is expensive and relatively high risk. It is unlikely that the pattern of contraceptive use will change radically in the next 10 years. No one method will be suitable for everyone, and individuals' preferences will probably change through their reproductive life. In the next five years more sophisticated systems for the delivery of steroid hormones, through or under the skin and into the uterus, will extend the range of options available. In five to 10 years new steroid antagonists such as antiprogestins will replace some current contraceptive methods, such as gestogen only pills, and probably lead to new approaches like a "once a month" pill. By 10-15 years, the dream of an effective safe male pill will probably become a reality, shifting the burden of responsibility for contraception more equally between men and women. Only then will women have truly achieved "the fifth freedom"—freedom from the burden of excessive fertility.[20]

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### *When I use a word ...*
### That's show business

The names of drugs are usually coined from words related to their chemical structures. For example, the full chemical name for a popular analgesic is *N*-acetyl-*para*-aminophenol. Simpler to use the British Approved Name, paracetamol, which is just a contraction of the full name, as is acetaminophen, the United States Adopted Name.

But some drug names have unusual origins. For instance, a few are derived from the entertainment business.

P Sensi and his colleagues at Lepetit Research Laboratories in Milan had the habit of giving new compounds nicknames, later substituting names that would be acceptable to scientific journals. Matamycin, for example (*Antibiot Chemother* 1959;9:76), was originally nicknamed Mata Hari. And when in 1957 they isolated a group of antibiotics from the fungus *Streptomyces mediterranei* (now called *Nocardia mediterranei*) they called them rifamycins, from the title of the French gangster film, *Rififi*, directed by Jules Dassin (1955). Rifampicin was the *N*-amino-*N'*-methylpiperazine (AMP) derivative—hence rif-amp-icin. Rififi is French argot for trouble, and the original title of the film was *Du Rififi Chez les Hommes*, which we might nowadays translate as *Men Behaving Badly*. The chief feature of the film was the half hour documentary-like sequence during which a bank robbery is staged in total silence. The startling effect of the return of sound to the screen was harnessed again by Dassin in another account of an unsuccessful heist, *Topkapi* (1964), based on Eric Ambler's novel *The Light of Day*.

Then there is opera. In 1977 several novel compounds were isolated from a substance known as bohemic acid complex III. Their discoverers named them marcellomycin, musettamycin, rudolphomycin, mimimycin, collinemycin, alcindoromycin, and schaunardimycin. Another compound was called bohemamine. Recall the plot of Puccini's opera *La Bohème*. Rodolfo and Marcello, poet and painter respectively, trying to work in their bitterly cold garret, are joined by their fellow lodgers, Colline (a philosopher) and Schaunard (a musician). Rodolfo meets a neighbour, Mimi, with whom he falls in love. Marcello's former lover, Musetta, gets rid of her ageing admirer, Alcindoro, and rejoins Marcello, but they later separate again. Rodolfo leaves Mimi too, but they are reunited just before she dies. Unfortunately, ignoring the symmetry of the plot, mimimycin is the 10 epimer of marcellomycin and collinemycin the 10 epimer of musettamycin—not the proper pairings at all. The spelling of rudolphomycin is also curious. In Henri Murger's original stories, *Scènes de la Vie de Bohème*, the poet's name is Rodolphe, while Puccini, being Italian, spelt the name Rodolfo. Perhaps the discoverers of these compounds (*J Nat Prod* 1980;43:242-58 and 1984;47:698-701) just made a mistake.

These -mycins are all anthracycline antibiotics, effective against cancers. But I wonder if they might have cured Mimi of her tuberculosis.

Jeff Aronson, *clinical pharmacologist, Oxford*

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# Feasibility of administering mifepristone as a once a month contraceptive pill

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**Many women find the idea of a once-a-month contraceptive pill an attractive concept. Mifepristone has been shown to be effective as a contraceptive if administered in the early luteal phase. We tested the contraceptive efficacy of 200 mg of mifepristone on day luteinizing hormone (LH) + 2 in a group of 32 women who used a fertility monitor to identify the LH surge. We also recruited a control group, comprising 20 women who were trying to conceive. In this group, 12 women conceived during a total of 50 control cycles (probability of pregnancy 0.25–0.32). Women in the treatment group contributed to a total of 178 cycles and there were two pregnancies (probability of pregnancy 0.01). An LH surge was not detected in 34 cycles (19.1%). In 20 cycles (11.2%) this was due to imperfect use while 14 were monitor method failures (7.9%). Treatment with mifepristone in the early luteal phase did not disrupt the cycle length but women reported slight vaginal bleeding in 15% of the cycles. The combination of a home-use fertility monitor with once-a-month administration of mifepristone (especially if mifepristone is administered at the early luteal phase) is an acceptable contraceptive option with minimal side effects. Unfortunately, it is difficult to envisage how an easier way of defining the correct timing, which required less compliance, could be devised.**

*Key words:* contraceptive/home use fertility monitor/LH surge/Mifepristone/once-a-month pill

## Introduction

Hormonal contraception is used by almost 100 million women world-wide. However, many women are deterred from using it because of perceived risks to health such as breast cancer or side effects such as weight gain. Most of the risks and the side effects are the results of prolonged exposure to steroids and many women, in a variety of cultural settings, find the idea of a pill which they need take only once each month, an attractive concept (Rimmer *et al.*, 1992; Glasier *et al.*, 1999).

Progesterone is essential for the establishment and maintenance of human pregnancy. The anti-progesterone mifepristone is a synthetic 19-norsteroid, which acts by blocking the action of progesterone at the receptor level (Spitz and Bardin, 1993), and thus, has multiple potential anti-fertility actions. When administered in the early luteal phase mifepristone retards endometrial development, without disturbing the timing of menses (Swahn *et al.*, 1988; Berthois *et al.*, 1991; Maentausta *et al.*, 1993). It also alters uterine contractility to a pattern more usually seen in the late luteal phase (Gemzell-Danielsson *et al.*, 1990). In 1993 Gemzell-Danielsson and colleagues conducted a pilot study in which a single dose of 200 mg of mifepristone was given in the early luteal phase [2 days following the surge of the lutenizing hormone (LH) in urine]. Out of 124 cycles in which coitus took place during the fertile period, only one pregnancy was observed (Gemzell-Danielsson *et al.*, 1993). There was no disruption of the timing of the subsequent menstrual bleed, although in 35% of the cycles slight vaginal bleeding was reported 2–3 days after treatment.

The main problem in developing a once-a-month contraceptive is finding a means that, both reliably and easily, identifies the start of the LH surge. Gemzell-Danielsson tried to solve this problem by using the LH sticks for home urine testing (Ovu-quick; Organon). In their study 12 out of 169 cycles were deemed to be anovulatory. However, it is not possible to determine if the LH surge truly was absent, or if the method failed to detect a surge. The woman may have read the test result wrongly or even failed to perform a test on the appropriate day.

Unipath (Bedford, UK) have developed a technology that can be used in the home to monitor changes in urinary hormones. This system comprises disposable test sticks and a hand held monitor, which together are used to detect changes in the levels of oestrone-3-glucuronide (E3G), a urinary metabolite of oestradiol, and LH, to indicate the potentially fertile days leading up to ovulation. The time from the first significant rise of LH in the urine to ovulation is reported to be around 24–48 h (Collins, 1996). The monitor thus should provide a convenient method of identifying the early luteal phase. Summary data for up to six consecutive cycles can be stored in the monitor memory and these data can be retrieved.

We investigated the contraceptive efficacy of 200 mg of mifepristone on day LH + 2 in a group of women who used this monitor to identify the LH surge.

## Materials and methods

This was a single centre study in healthy female volunteers, approved by the Lothian Research Ethics Committee. All subjects gave written informed consent to participation. Fifty-two sexually active women, with regular (25–32 day) menstrual cycles were recruited from a large Family Planning Clinic in Edinburgh. If the women had a significant medical condition or if they or their partners had a history of fertility problems, they were excluded from the study.

### *Treatment group*

Thirty-two women were recruited to the treatment group. None had been taking hormonal preparations within the 2 months prior to the start of the study and all had had at least two spontaneous menstrual periods since stopping hormonal contraception. All women underwent screening at the time of recruitment including a routine physical and gynaecological examination. A venous blood sample was taken for full blood count, serum biochemistry and liver function. The study started on day 1 of the menstrual period following screening, and lasted for up to seven consecutive menstrual cycles in which subjects took 200 mg mifepristone once per month.

### *Control group*

The control group consisted of 20 healthy women with regular menstrual cycles who were trying to become pregnant (for less than 6 months prior to the enrolment in to the study) and hence, were not using contraception. They were provided with a monitor, which they used according to the manufacturer's instructions. Women were advised that their chance of conception would be higher if they were to have sexual intercourse during the fertile period, identified by the monitor. The controls took part in the study until pregnancy occurred or for a maximum of six cycles if they did not conceive.

### *Procedure*

All subjects and controls were provided with a home use hormone monitoring system (Unipath, Bedford, UK). The system comprises a hand-held monitor and disposable dual-assay urine test sticks, and is used to simultaneously detect LH and E3G levels in early morning urine. The monitor optically measures the intensity of the lines that form on the test sticks after sampling, and the system will delineate three levels of fertility (Low, High and Peak Fertility) according to the optical signal changes detected. Low fertility will be displayed from day 1 of the cycle, until the hormone levels rise above the baseline levels. A change from low to high fertility is triggered by detection of elevated E3G levels, to concentrations typically between 20 and 30 ng/ml. The change from high to peak fertility is triggered by the detection of an LH surge, typically with a concentration >30 IU/l.

Peak fertility is displayed on the day of the LH surge and on the following day. Subsequently high fertility is displayed for 1 day prior to a return to low fertility. At the start of each menses, the subjects pressed the 'm' button on their monitor to initiate that cycle of use, at a time suitable for testing the first urine of the day. For the rest of the month, the subjects were required to consult the monitor display each morning (3 h either side of the time when 'm' button was set) to determine whether they needed to perform a test that day. Beyond this 6 h time window the monitor would not accept a test. The system requests one test every day for up to a total of 10 or 20 tests, depending on the length of the woman's cycle, and the timing of her LH surge. Embedded software within the monitor collects and analyses data from each cycle to identify and display fertility status to the user, and stores data for several months.

Mifepristone (Laboratories Exelgyn, Paris, France) was taken 2 days after the day of the first day of peak fertility (LH surge). With each cycle, subjects followed the same protocol, and were reviewed by the investigator monthly, on day LH + 2. Just before taking the 200 mg tablet of mifepristone, a venous blood sample was taken, and later assayed for progesterone. At the beginning of the study, if the LH surge was not identified by day 21 of the cycle, the subject was instructed to continue testing, but mifepristone was not given in that cycle. The subject was also advised to use barrier contraception from day 21 until the onset of the next menses. After the second pregnancy (which occurred due to a failure in detecting an LH surge), we changed this practice. We calculated the estimated day of LH surge for each month based on information from the previous cycles. If the women did not detect an LH surge either within 3 days after the anticipated day of LH surge or by day 19, a blood sample was taken for rapid serum progesterone assay. If the progesterone level was >5nmol/l and if the woman was at risk of pregnancy, mifepristone was administered.

All subjects and controls kept a menstrual record card, recording all vaginal bleeding experienced during the study and the days on which they had sexual intercourse. Subjects also marked the first day of the peak fertility as identified by the monitor and the day of taking the study medication.

If menstruation was overdue by more than one week the investigator performed a pregnancy test. Provided this was negative, the subject continued in the study and the next cycle was deemed to start with the onset of menses. Since the effect of mifepristone taken in very early pregnancy is unknown, and teratogenic effects could not be ruled out, women who would not consider terminating any pregnancy were not recruited to the treatment group.

At the end of the study, the subjects attended for a final visit, when a routine physical and gynaecological examination was performed. Full blood count, serum biochemistry and liver function were reassessed.

The following definitions were created for the purpose of the study.

**Imperfect use:** was defined as failure to detect an LH surge through performing the test incorrectly (e.g. dipping a test stick in urine 30 or more min before it being read by the monitor), or failing to perform tests as requested by the monitor.

**Monitor method failures:** were defined as failure to detect an LH surge despite performing all tests as requested.

**High fertile days:** days preceding the urinary LH surge as indicated by the monitor to be potentially fertile.

**Peak fertile days:** The first day of a significant rise in urinary LH detected by the monitor, and the following day.

**The fertile period:** of the cycle was defined as 3 days before until 2 days after the urinary LH surge (LH–3 to LH+2).

**Exposure cycles:** were cycles in which women reported having sexual intercourse at least once during the fertile period.

### *Statistical analysis*

Cycle lengths and serum progesterone concentrations were compared by two-sample *t*-tests. Confidence limits for efficacy were derived from confidence limits for relative risk calculated by the Greenland and Robins method (Greenland and Robins, 1985).

## Results

Table I shows the demographic characteristics of the women who took part in the study.

Table I. Demographic data.

| | Treatment group ($n$ = 32) | Control group ($n$ = 20) |
|---|---|---|
| **Age** | | |
| Range | 18–39 | 26–40 |
| Mean (± SD) | 30 (± 5.4) | 32.9 (± 4.5) |
| **BMI** | | |
| Range | 19–38 | 21–29 |
| Mean (± SD) | 23.6 (± 4.3) | 23.8 (± 2.7) |
| Smokers (%) | 7 (21.9) | 1 (5) |
| Non-smokers (%) | 21 (65.6) | 16 (80) |
| Ex-smokers (%) | 4 (12.5) | 3 (15) |
| **Previous pregnancies** | | |
| 1+ (%) | 19 (59.4) | 14 (70) |
| Never been pregnant (%) | 13 (40.6) | 6 (30) |
| Ever abortion (%) | 15 (46.9) | 5 (25) |
| Married/Co-habiting (%) | 28 (87.5) | 20 (100) |
| Single (with a regular boy friend) (%) | 4 (12.5) | 0 (0) |

The women in treatment group were slightly younger (mean age 30 years) than those in the control group (mean age 32.9 years). Otherwise there were no differences between subjects and controls.

### *The probability of pregnancy in the control group*

Twenty women were recruited to the control group and three withdrew before completing the study. Two withdrew from the study as they found using the system 'too stressful' and one withdrew because she no longer wished to plan a pregnancy. Data were collected from 50 control cycles during which 12 pregnancies occurred. Average frequency of intercourse was 1.7 episodes per week in the 39 control cycles in which the women kept a record of their sexual activity. In 37 cycles women had intercourse at least once during the fertile period (FP). In two cycles intercourse did not occur during the FP, while in 11 cycles the exposure status was unknown, as women failed to keep a record of sexual activity. Eight pregnancies occurred in the first exposure cycle.

If we assume that all 11 cycles from which information on sexual activity was lacking were exposure cycles, the probability of pregnancy was 0.25. However if those cycles were all non-exposure cycles, the probability of conception would be 0.32. Therefore among the control group the overall probability of pregnancy if sexual intercourse took place at least once during the fertile period lies between 0.25–0.32.

### *Contraceptive efficacy of the method*

Thirty-two volunteers were treated with a single dose of 200 mg of mifepristone administered in the luteal phase of the cycle as their sole method of contraception between one and seven cycles. They contributed a total of 178 cycles, and in 167 cycles mifepristone was administered. Eight women withdrew from the study before completion; two women moved out of the area, three ended their relationship, two conceived during the study and one lost confidence in the method.

Two clinical pregnancies occurred in the 178 cycles studied. The first pregnancy was a true treatment failure, which occurred in a woman (para 1) who took mifepristone on day 14 (LH + 2) of her first treatment cycle. She opted for a surgical termination of pregnancy, which was performed at 8 weeks of gestation (confirmed by ultrasound scanning). In the second woman (para 3), an LH surge was not identified in her third study cycle hence she did not receive treatment with mifepristone, menses did not occur and on day 37 after her last menstrual period an ectopic pregnancy was diagnosed and treated surgically. In a third woman a biochemical pregnancy was diagnosed (serum βHCG only rising to 34 IU/l), which was spontaneously and completely aborted by day 34 of the third study cycle after taking mifepristone on day 14 (LH + 2). This woman continued in the study and completed six treatment cycles.

The mean frequency of sexual intercourse was 1.8 episodes per week in 167 treatment cycles in which sexual activity was recorded. If we assume the probability of pregnancy in the treatment group is similar to the control group (0.25–0.32), the expected number of clinical pregnancies during the 178 cycles (in which 140 were exposure cycles) studied should be between 35–48.3. The observed number was two. Therefore, the efficacy of the method is 94.3% (95% confidence interval 75.4–98.7) – 95.9% (95% CI 82.5–99.0).

When calculating the efficacy of the method, we excluded the 29 cycles during which women were not exposed to a risk of pregnancy, and the three cycles in which mifepristone was taken in the follicular phase.

### *Contraceptive efficacy of luteal phase administration of mifepristone*

In 145 cycles in which mifepristone was taken in the early luteal phase (within 2 days of the urinary LH surge) 117 were exposure cycles (Table II). Exposure status was unknown in eight cycles and in 20 cycles women were not at risk of pregnancy. In the 117 exposure cycles, there was only one clinical pregnancy.

In 19 (10.7%) cycles, no LH surge was declared by the monitor but mifepristone was given as coitus had taken place during the fertile period of the cycle (calculated according to the usual cycle length and usual day of LH surge). Occurrence of ovulation was confirmed by serum progesterone of >5 nmol/l in all 19 cycles and treatment was administered prior to day 21 of the cycle in each case [between day 13–21 of the cycle, mean 16.9 (SD ± 2.1) days]. There were no pregnancies in these cycles.

If the probability of pregnancy in all exposure cycles in the study is 0.25–0.32 (the same as that of the control group), between 34–46 clinical pregnancies would be expected in the 136 ovulatory cycles in which mifepristone was taken in the luteal phase. The observed number was one. Hence, the contraceptive efficacy of luteal phase mifepristone is between 97.1% (95% CI 78.00–99.6) – 97.8% (95% CI 83.9–99.7).

### *Performance of the home use hormone monitor*

In 140 treatment cycles an LH surge was identified by the monitor, which equates to 90.9% LH surge detection when calculated for perfect use cycles; and 80.5% when imperfect use cycles are also included in the total. In 127 cycles this

**Table II.** Treatment cycle details.

| | Total no. cycles | Exposure cycles | Unknown exposure | No Exposure |
|---|---|---|---|---|
| Mifepristone administered | 167 | 136 | 8 | 23 |
| In follicular phase | 3 | 0 | 0 | 3 |
| In luteal phase | 164 | 136 | 8 | 20 |
| Early luteal phase | 145 | 117 | 8 | 20 |
| LH + 2 | 127 | 100 | 7 | 20 |
| LH + 1 | 17 | 16 | 1 | 0 |
| LH + 0 | 1 | 1 | 0 | 0 |
| In luteal phase (unknown LH status) | 19 | 19 | 0 | 0 |
| Mifepristone not given | 11 | 5[a] | 0 | 6[b] |
| Total | 178 | 140 | 8 | 29 |

[a]LH surge missed, at risk of pregnancy but after day 21.
[b]Anovulatory cycle $n = 1$, LH surge missed and no risk of pregnancy $n = 5$).

was confirmed by a subsequent rise in serum progesterone of >5 nmol/l in the early luteal phase. This information was not available from nine cycles (blood samples lost or not collected). In the remaining four cycles serum progesterone was between 2–5 nmol/l, 1 or 2 days following the urinary LH surge as detected by the monitor. This may have been due to an early detection of the first significant rise in urinary LH. None of these five cycles were prolonged after taking mifepristone, hence it is unlikely that they were anovulatory.

There was a total of 38 (21.3%) cycles in which an LH surge was not detected. Among them, one (0.6%) was an anovulatory cycle, defined by serum progesterone not rising above 5 nmol/l in the mid-luteal phase. In three (1.7%) other cycles we administered mifepristone on day 19, before the monitor had identified an LH surge. Serum levels of progesterone (taken on the day of administering mifepristone) confirmed that in these cycles mifepristone was administered in the follicular phase. All three cycles were prolonged (43–52 days).

In the remaining 34 cycles an LH surge probably occurred (as suggested by a rise in serum progesterone of >5 nmol/l) but was not identified by the monitor. Fourteen were missed due to monitor method failure (7.9%) and 20 were a consequence of imperfect use of the system (11.2%).

### *Cycle length*

Mifepristone when given in early luteal phase did not significantly affect the cycle length ($P = 0.35$). The mean of the usual cycle length was 28.3 days (SD ± 1.3) and during the treatment cycles it was 28.0 days (SD ± 1.9).

### *Side effects*

Women kept a record of vaginal bleeding in 139 out of the total 144 cycles where mifepristone was taken on LH + 2. Mifepristone induced vaginal bleeding within 72 h in 21 cycles (15%). In a further 19 cycles, our volunteers took mifepristone in the luteal phase but the LH status was not known. In 17 of those cycles (>89%), mifepristone induced a vaginal bleed.

Serum progesterone values in blood samples taken just prior to mifepristone administration were available for 136 cycles. The mean serum progesterone value was significantly ($P < 0.0001$) higher in those cycles where mifepristone induced bleeding when compared to the mean value for the cycles without bleeding [21.72 (SD ± 9.04) nmol/l versus 13.33 (SD ± 6.23) nmol/l].

Two women spontaneously reported improvement of their pre-menstrual symptoms during cycles in which mifepristone was administered, while one reported worsening. In one woman hepatic alanine aminotransferase (ALT) was elevated at 103 IU/l (normal range 10–40 IU/l) at the end of the study but returned to normal within 2 months. One woman complained of diarrhoea 12 h post mifepristone in one cycle, three reported menstrual cramping within 72 h of taking mifepristone; two women reported a reduction in menstrual blood loss.

## Discussion

A single dose of 200 mg of mifepristone administered once a month is an effective contraceptive method with an overall efficacy of 95% increasing to 97% if administered at the correct time (i.e. the early luteal phase). Thus our results are in agreement with the findings of a previous study (Gemzell-Danielsson *et al.*, 1993).

One criticism of previous work in this field has been the lack of a suitable control group for the subjects studied. Unlike the Gemzell-Danielsson study, we were able to compare the results with a contemporaneous control group using the same methodology in the same cultural setting. In this control group, if sexual intercourse took place on a fertile day the probability of a pregnancy was 0.25–0.32. The calculated probability of pregnancy in a cohort of couples monitored during a study of natural family planning (WHO, 1983) was 0.486 if intercourse took place 3 days prior to and a day after the peak day of mucus discharge. The difference in the probability of pregnancy between our study and a variety of other published series (Table III) may be explained by the fact that we have extended our definition of the fertile period to 6 days (3 days prior to the urinary LH surge until 2 days after). Other authors (Wilcox *et al.*, 1995) have calculated that the likelihood of conceiving during an ovulatory cycle to be 0.37 (95% confidence interval 0.31–0.48) if daily sexual intercourse took place during a 6 day fertile period (four days before and a day after ovulation). The lower frequency of intercourse in

**Table III.** Probability of clinical pregnancy.

| | No. of exposure cycles | No. of pregnancies | Probability of pregnancy |
|---|---|---|---|
| Wilcox *et al.*, 1995[b] | 129 | 34 | 0.26 |
| Our control group[b] | 37–48 | 12 | 0.25–0.32 |
| Our treatment group[b] (monitor + mifepristone) | 140–151 | 2 | 0.01 |
| Our treatment group[b] (mifepristone in luteal phase) | 136–143 | 1 | 0.007 |
| Gemzell-Danielsson *et al.*, 1990[a] | 124 | 1 | 0.008 |
| WHO study[a] | 72 | 35 | 0.48 |

[a]The length of the fertile period defined as 4 days.
[b]The length of the fertile period defined as 6 days.

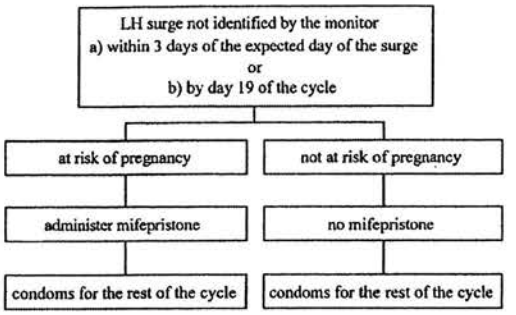


**Figure 1.** Algorithm for administering mifepristone when the LH surge is not identified

our group (untimed intercourse averaging 1.7 per week) may also explain the lower probability of pregnancy.

The limiting factor in this once-a-month approach to administering anti-progesterone is the accurate detection of the LH surge. Clearly, the failure to detect accurately the LH surge has a big impact on the overall effectiveness of the method. Using laboratory assay of LH in blood or urine to identify ovulation is neither practical nor convenient for long term use in the general population. The monitor provided us with an opportunity to overcome these problems. Gemzell-Danielsson *et al.* (1993) reported 49% accuracy using home LH detection sticks (Gemzell-Danielsson *et al.*, 1993). Although the monitor performed better (over 80.5% accuracy), both of these methods remain below the required standard. We studied 32 women over a total of 178 cycles. Imperfect use of the system accounted for failure to identify an LH surge in 11.8% cycles while 7.9% were due to monitor method failure. Compliance difficulties are associated with all contraceptives and non-compliance in ~12% of cycles is probably no worse than with any other method which demands action from the user, for example, compliance rates reported from oral contraceptive pill users range from 3.4–100% (Wheble *et al.*, 1981; Molloy *et al.*, 1985; Hamilton and Hoogland, 1989). Although our study population consisted of women who were motivated and committed and some of them already had experience in using natural family planning methods, they found the short, inflexible testing window set on day 1 of the cycle to be particularly demanding. This is inconsistent with couples using the monitor in order to get pregnant (Bonnar *et al.*, 1999). The prevalence of imperfect use is likely to rise in the general population compared with that typical of a research study.

During the course of the study we developed an algorithm (Figure 1) for the administration of mifepristone if an LH surge was not identified. In 19 exposure cycles (out of 28 cycles in which an LH surge was not identified) mifepristone was administered using this algorithm and there were no pregnancies. Given that the methods available to be used in real life to time the administration of mifepristone cannot be 100% accurate, such an algorithm will be essential to deal with a missed LH surge.

In our study, mis-timed administration of mifepristone led to predictable effects. When administered during the proliferative phase of the menstrual cycle, mifepristone inhibited follicular development, and delayed the mid cycle LH surge, leading to a delay in ovulation and subsequent prolongation of the menstrual cycle (Liu *et al.*, 1987; Luukkainen *et al.*, 1988; Swahn *et al.*, 1988). Ovulation may occur later in that cycle, leaving women at risk of conception. In our study, when administered in the late follicular phase (in error) in three cycles, mifepristone prolonged the cycle length (43–52 days). The women were advised to use condoms for the remainder of that cycle and none of the three cycles resulted in pregnancy.

Administration of mifepristone in the mid or late luteal phase induces a bleed within a few days of treatment, which may or may not be followed by a second bleed at the time of expected menstruation (Shoupe *et al.*, 1987; Swahn *et al.*, 1988). In our study, in 17 out of the 19 cycles where mifepristone was taken after ovulation (the LH status unavailable and probably later than on LH + 2), intermenstrual vaginal bleeding occurred (89.5%). Moreover, there was an increased risk of bleeding seen in those women who may have taken mifepristone slightly later in the LH + 2 window. The mean serum progesterone concentration was significantly higher in those women who had bleeding after taking mifepristone within LH + 2, when compared with those who did not. The higher serum progesterone value in some on LH + 2, could be due to a delayed identification of the first significant rise in urinary LH, or because of a more rapid increase in serum progesterone due to early ovulation. Nevertheless, in our group of women, in all cycles where mifepristone induced a vaginal bleed, a second bleed occurred at the time of the expected menses. Therefore, while the bleeding may have been inconvenient, it did not jeopardise efficacy or continued use of the method. There was less inter-menstrual bleeding (15% of the cycles) reported in our study when mifepristone was taken within LH + 2, less than half of that reported by Gemzell-Danielsson *et al.* (32%) (Gemzell-Danielsson *et al.*, 1993). This is possibly due to the fact that the majority of women in our study received mifepristone at the correct time. In their study, in 51% of the cycles, mifepristone was taken between 3 and 5 days after the LH surge.

In conclusion, the use of the combination of home use

fertility monitor with once-a-month administration of mifepristone (especially if mifepristone is administered at the early luteal phase) is an attractive contraceptive option with minimal side effects. However, to be an effective contraceptive method, the women have to be committed to using a device, which identifies the LH surge, in order that the pill can be taken at the correct time in the cycle. Whilst this regimen may be acceptable to motivated women, it may be regarded as too complicated for others to adopt on a routine basis. There was evidence of such non-compliance in this study, with 11.2% of LH surges being missed as a consequence of imperfect use of the monitor. Unfortunately, it is difficult to envisage how an easier way of defining the correct timing, which obligated less compliance, could be devised.

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# MIFEPRISTONE (RU 486) COMPARED WITH HIGH-DOSE ESTROGEN AND PROGESTOGEN FOR EMERGENCY POSTCOITAL CONTRACEPTION

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**Abstract** *Background.* Mifepristone (RU 486) is a synthetic steroid with potent antiprogestational and antiglucocorticoid properties that provides an effective medical method of inducing abortion in early pregnancy. Since progesterone is essential for implantation, we tested the use of mifepristone for emergency postcoital contraception.

*Methods.* We studied 800 women and adolescents requesting emergency postcoital contraception who had had unprotected intercourse within the preceding 72 hours. A total of 398 women and adolescents were randomly assigned to treatment with 100 μg of ethinyl estradiol and 1 mg of norgestrel, each given twice 12 hours apart (standard therapy), and 402 women and adolescents were randomly assigned to receive 600 mg of mifepristone.

*Results.* None of the women and adolescents who received mifepristone became pregnant, as compared with four of those who received standard therapy; the difference in failure rates between the two regimens was not statistically significant. The number of pregnancies in each group was significantly lower than the number expected according to calculations based on the day of the cycle during which intercourse had taken place ($P<0.001$). In many subjects the stage of the cycle as calculated by menstrual history was inconsistent with measurements of plasma progesterone or urinary pregnanediol excretion. The subjects treated with mifepristone reported less nausea (40 percent vs. 60 percent) and vomiting (3 percent vs. 17 percent) on the day of treatment, as well as lower rates of other side effects, than the subjects treated with the standard regimen, but they were more likely to have a delay in the onset of the next menstrual period (42 percent vs. 13 percent).

*Conclusions.* Mifepristone is a highly effective postcoital contraceptive agent that, if used more widely, could help reduce the number of unplanned and unwanted pregnancies. (N Engl J Med 1992;327:1041-4.)

DESPITE the availability of highly effective methods of contraception, many conceptions are unplanned.[1] Many women who request an abortion have become pregnant as a result of either the lack of forethought or contraceptive failure.

The report by Yuzpe and Lancee[2] that a combination of a large dose of estrogen and a progestogen prevented pregnancy after intercourse led to the development of the now standard regimen of 100 μg of ethinyl estradiol and 1 mg of norgestrel, each given twice 12 hours apart, for emergency contraception. Fasoli et al.,[3] in a review of the results of published studies of this regimen, reported a wide variation (from 0.2 to 7.4 percent) in the rate of failure. The side effects of the combined administration of estrogen and progestogen are those commonly associated with estrogen; most studies report nausea in 50 percent of women and vomiting in up to 25 percent. When these symptoms occur within the first 12 hours after treatment is initiated, they may impair compliance and efficacy. The postcoital insertion of an intrauterine device is highly effective in preventing pregnancy (failure rate, 0.1 percent), but the process of insertion is invasive and associated with side effects. Other oral agents used for this purpose include danazol and high-dose levonorgestrel, but the failure rates of these agents have been as high as 10 percent.[4,5]

Progesterone is necessary for the formation of secretory endometrium and therefore for the establishment and maintenance of pregnancy. Mifepristone (RU 486) is a synthetic steroid with potent antiprogestational and antiglucocorticoid activity. When given in combination with a prostaglandin, it has proved to be a safe, convenient alternative to surgical termination of early pregnancy.[6-9] Reflecting the importance of progesterone in many biologic processes, mifepristone has many other potential uses, such as the inhibition of ovulation,[10,11] prevention of the development of secretory endometrium,[12] induction of labor,[13] and treatment of endometriosis and breast cancer.[14]

We compared the efficacy and side effects of a 600-mg dose of mifepristone with those of the standard regimen of estrogen and progestogen as emergency

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postcoital contraceptive agents in a randomized trial of 800 women and adolescents. A preliminary report describing the results in the first 379 subjects in this study has been published.[15]

## Methods

We studied 800 women and adolescents ranging in age from 16 to 45 years who were recruited from the Dean Terrace Centre in Edinburgh (752 subjects) and the Accident and Emergency Department of the Royal Infirmary of Edinburgh (48 subjects). All the women and adolescents were seeking emergency postcoital contraception. All had a history of regular menstrual cycles of 21 to 35 days for the preceding three months, were seen within 72 hours after a single act of unprotected intercourse, and were willing to use a condom or abstain from intercourse for the rest of the current cycle. We excluded women and adolescents who were taking an oral-contraceptive preparation, had a medical contraindication to the standard estrogen–progestogen regimen (a history of cardiovascular disease, thromboembolism, or liver disease), were regularly using prescription drugs (anticonvulsant medications or insulin), were certain that they would continue with the pregnancy if emergency contraception failed, or would be unavailable for follow-up.

The project was approved by the local ethics committee, and written informed consent was obtained from each subject, who was informed that there was a risk of failure no matter which treatment she received. Mifepristone was supplied by the World Health Organization, and the use of the drug for emergency contraception was approved by the Medicines Control Agency of the United Kingdom.

A careful menstrual history was obtained from each subject, and the interval between intercourse and presentation was recorded. The estimated day of ovulation was calculated as being 14 days before the estimated day of onset of the next menstrual period; each subject's usual cycle length was taken into account. On the basis of these data we determined whether a subject was treated at midcycle (one day before or after ovulation), in the follicular phase of the cycle (two or more days before ovulation), or in the luteal phase of the cycle (two or more days after ovulation). A pelvic examination was undertaken only if clinically indicated. Each subject's height and weight were recorded.

To allow for differences in fertility and therefore possible differences in failure rates with age, the women and adolescents were divided into three age groups: 16 to 25 years, 26 to 34 years, and 35 to 45 years. The women and adolescents in each age group were randomly assigned to receive either 600 mg of mifepristone as a single dose taken at the time of enrollment or two 100-$\mu$g doses of ethinyl estradiol and two 1-mg doses of norgestrel, the second dose of each being taken at home 12 hours after the first.

Blood or urine samples were collected at the time of enrollment for the measurement of the plasma progesterone concentration and urinary pregnanediol excretion. Each subject was asked to complete a diary chart recording the occurrence and severity of nausea, vomiting, breast tenderness, headache, and vaginal bleeding each day for seven days after treatment, and each made an appointment to return to the clinic within five days of the expected date of the next menstrual period. Each subject was given a stamped, addressed envelope in which to return the diary chart and to inform the clinic of the date of the next menstrual period should she be unable to return. Attempts were made to contact the women and adolescents who did not return or mail in a completed diary chart. After three unsuccessful attempts the subject was classified as lost to follow-up.

At the follow-up visit the diary chart and date of menstrual bleeding were checked by a member of the clinic staff. If menstrual bleeding had not occurred, blood was taken for the measurement of the beta subunit of chorionic gonadotropin in the plasma and another appointment was made. The subject returned for additional follow-up every two weeks until she had a normal menstrual period.

### Assay Methods

Urinary pregnanediol-3-glucuronide was measured by enzyme-linked immunosorbent assay.[16] The sensitivity of the assay was 0.17 ng per milliliter (0.5 nmol per liter), and the interassay and intraassay coefficients of variation were 12 percent and 10 percent, respectively. Plasma progesterone was measured by a radioimmunoassay in which 1-anilino-8-naphthalenesulfonate (pH 4.0) was used to displace progesterone from plasma binding proteins.[17] The interassay and intraassay coefficients of variation were 10 percent and 8 percent, respectively. Plasma progesterone concentrations of more than 3 ng per milliliter (>9 nmol per liter) or urinary pregnanediol excretion in excess of 0.5 mmol per mole of creatinine (>2.17 mg per gram of creatinine) were considered to be compatible with ovulation; plasma progesterone concentrations ranging from 1.6 to 2.9 ng per milliliter (5 to 9 nmol per liter) or urinary pregnanediol excretion of 0.3 to 0.4 mmol per mole of creatinine (1.3 to 1.7 mg per gram of creatinine) were considered periovulatory; and plasma progesterone concentrations below 1.6 ng per milliliter (<4 nmol per liter) or urinary pregnanediol excretion below 0.2 mmol per mole of creatinine (<0.9 mg per gram of creatinine) were considered consistent with the absence of ovulation.

### Statistical Analysis

Fisher's exact test (two-tailed) was used to compare the efficacy of the two regimens, and chi-square tests were used to compare the incidence of side effects in the two groups.

## Results

A total of 402 women and adolescents were treated with mifepristone, and 398 were treated with the standard regimen of ethinyl estradiol and norgestrel. Of the 800 women and adolescents, 566 were 16 to 25 years of age, 192 were 26 to 35 years of age, and 42 were 36 to 45 years of age. Twenty-six women and adolescents (3 percent) were lost to follow-up, of whom seven had had intercourse within three days before or after the estimated day of ovulation and might be considered genuinely at risk for conception; three of these subjects received mifepristone. A further 16 women and adolescents failed to reply to letters or telephone calls but returned for follow-up within three months after treatment. Although unable to recall the date of menstruation, none had become pregnant.

### Efficacy

Four women became pregnant, all of whom had received the standard regimen; there were no mifepristone failures. The overall failure rate in the standard-therapy group was 1.0 percent (95 percent confidence interval, 0.3 to 2.5 percent). All four women chose to have the pregnancy terminated. The difference in failure rates between the standard regimen (1.0 percent) and mifepristone (0 percent) was not statistically significant ($P = 0.12$). The characteristics of the four women who conceived are shown in Table 1.

Accurate cycle data were obtained for 733 women and adolescents, of whom 322 (44 percent) had had intercourse within three days before or after the estimated day of ovulation. One hundred sixty-seven of these subjects received mifepristone. All 4 of the women who became pregnant were among the 155 subjects in this group of 322 who were treated with the standard regimen, for a failure rate of 3 percent.

### Side Effects

A total of 693 women and adolescents returned completed diary charts. The incidence of side effects is shown in Table 2. All side effects were significantly

Table 1. Characteristics of the Four Women Who Became Pregnant after Receiving the Standard Regimen for Postcoital Contraception.

| Subject No | Age | Body-Mass Index* | Day of Intercourse/Normal Cycle Length | Time from Intercourse to Treatment | Plasma Progesterone† |
|---|---|---|---|---|---|
| | *yr* | | *days* | *hr* | *ng/ml* |
| 1 | 32 | 25 | 13/28 | 13 | 1.0 |
| 2 | 25 | 26 | 15/28 | 14 | 1.6 |
| 3 | 23 | 22 | 15/28 | 40 | 6.6 |
| 4 | 24 | 23 | 15/30 | 40 | 1.3 |

*Body-mass index is expressed as the weight in kilograms divided by the square of the height in meters.

†To convert values for progesterone to nanomoles per liter, multiply by 3.18.

(P<0.001) more frequent among the subjects treated with the standard regimen, and more of the women and adolescents who were treated with mifepristone reported having no side effects (P<0.001). Among the subjects who had nausea on the day of treatment, 17 percent of those who received the standard regimen described the nausea as being severe, whereas only 2 percent of those who received mifepristone did so.

### Timing of Menses

The timing of the onset of menstrual bleeding after emergency postcoital contraception is shown in Table 3. A subject who reported bleeding within three days before or after the expected day of menstruation was described as having menstruated on time. Significantly more (P<0.001) of the women and adolescents who were treated with mifepristone had a delay in the onset of menstruation (range, 4 to 63 days).

## Discussion

Most published studies of the efficacy of postcoital contraception report failure rates in terms of the number of pregnancies as a function of the total number of women treated, and do not report the number lost to follow-up. Not all women given emergency postcoital contraception are genuinely at risk for pregnancy, since unprotected intercourse that occurs in the early follicular phase or in the luteal phase of the cycle is unlikely to result in conception. On the basis of cycle dates, 44 percent of the women and adolescents in this study were treated within three days before or after the estimated day of ovulation. Silvestre et al.[18] argued that the true failure rate should take into account the timing of unprotected intercourse and therefore the probability that a pregnancy will occur. Using a table that provides a probability of pregnancy for each day of the cycle,[19] Silvestre et al.[18] recalculated the failure rates of the standard estrogen and progestogen regimen reported in a number of studies. Failure rates reported as ranging from 0.2 to 5 percent on the basis of the number of women treated ranged from 6 to 44 percent when the table was used and the probability of pregnancy taken into account. Using the table in the same way, we calculated that we should have expected 23 pregnancies in each treatment group in our study, which would mean a failure rate of 17 percent for the standard regimen and, of course, 0 percent with mifepristone. Both regimens resulted in significantly fewer pregnancies than would have been expected had no treatment been given (P<0.001).

The validity of using the table depends on the accuracy of the menstrual-cycle data. The measurements of plasma progesterone or urinary pregnanediol in 780 women and adolescents on the day of treatment provided the opportunity to determine whether the cycle data were compatible with the biochemical evidence of ovulation. Of the 368 women believed on the evidence of cycle data to be in the luteal phase of the cycle, 187 (51 percent) had a plasma progesterone or urinary pregnanediol value indicating that ovulation had not occurred. Forty-four of the 205 women and adolescents (21 percent) considered to have been treated in the follicular phase had biochemical evidence of ovulation. Ninety women and adolescents who had intercourse four to nine days after the estimated day of ovulation, and who were therefore excluded from our calculations of the fertile phase of the cycle, had not in fact ovulated when they were treated and could therefore have been genuinely at risk for pregnancy. Most women do not keep a record of their menstrual periods, and it is well recognized that estimated dates are likely to be inaccurate. In our study the dates appeared more likely to be accurate in the follicular phase of the cycle when menses had recently occurred.

Regardless of the method by which failure rates are calculated, the fact remains that none of the women and adolescents who were treated with mifepristone conceived. Although the difference in the failure rates was not statistically significant, mifepristone was unquestionably as effective as the standard estrogen–progestogen regimen as emergency postcoital contraception. Although the subjects were aware of which treatment they received, they were not advised that there might be any difference in side effects. It is clear, however, that mifepristone was associated with fewer side effects. Moreover, since it was taken as a single

Table 2. Incidence of Side Effects among Women and Adolescents Treated with Mifepristone or the Standard Estrogen–Progestogen Regimen for Postcoital Contraception.*

| Side Effect | Mifepristone (N = 347) | Standard Regimen (N = 346) | P Value |
|---|---|---|---|
| | *number (percent)* | | |
| No symptoms | 132 (38) | 45 (13) | <0.001 |
| Nausea on day of treatment | 137 (40) | 207 (60) | <0.002 |
| Nausea after day of treatment | 98 (28) | 184 (53) | <0.001 |
| Vomiting on day of treatment | 9 (3) | 59 (17) | <0.001 |
| Headache at any time | 170 (49) | 242 (70) | <0.001 |
| Breast tenderness at any time | 94 (27) | 158 (46) | <0.001 |

*A total of 693 women and adolescents completed diary charts: 347 treated with mifepristone and 346 treated with the standard regimen.

Table 3. Timing of Menses among Women and Adolescents after Postcoital Contraceptive Treatment with Mifepristone or the Standard Regimen.*

| Onset of Menses | Standard Regimen | Mifepristone | P Value |
|---|---|---|---|
| Early | 142 | 76 | <0.001 |
| On time† | 166 | 111 | <0.001 |
| Late | 45 | 137 | <0.001 |

*Sixteen women and adolescents were excluded because they could not recall the date of menstruation.

†Menses considered to be on time were those that occurred within three days before or after the expected date.

dose, there was no possibility of noncompliance if side effects occurred.

The only apparent disadvantage of mifepristone was that more of the women and adolescents who took it had a delay in the onset of the next menstrual period — an occurrence that would undoubtedly be stressful to a woman who was worried that she might be pregnant. In contrast to the standard regimen, however, it is possible to make some prediction about the timing of the onset of the next menses after the administration of mifepristone. Of the women and adolescents who were treated with mifepristone in whom both cycle and biochemical data suggested that they were in the follicular phase, 52 percent had bleeding more than four days after the expected date of their next menstrual period, indicating that mifepristone inhibited ovulation.[10] Of those who were treated in the luteal phase (confirmed biochemically), 84 percent either bled before the estimated date of their next menstrual period or menstruated on time. The administration of mifepristone in the luteal phase is associated with early bleeding in 100 percent of women.[20,21]

In conclusion, we confirmed our preliminary report[15] that mifepristone is an effective postcoital contraceptive agent with advantages over the standard estrogen–progestogen regimen. A dose of 600 mg is probably higher than necessary, but no studies have yet been done to determine the optimal dose. The real problem with emergency postcoital contraception is not its failure rate or its side effects but the fact that so few women and adolescents who have had unprotected intercourse actually use it.

Mifepristone has been a center of controversy since the report of the initial clinical study demonstrating its efficacy as an abortifacient agent.[13] Research into alternative uses of mifepristone is severely restricted in many countries, including the United States, largely as a result of the activities of those who are opposed to abortion. The results in this paper demonstrate that the drug has the potential to avert unwanted and unplanned pregnancy. More widely available contraceptive services that included mifepristone as a postcoital agent would help reduce the demand for therapeutic abortion.

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# Do women want a once-a-month pill?

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**The attitudes of women of reproductive age in Scotland, Romania and Slovenia to the idea of a contraceptive pill which is taken only once each month or only when menses are delayed was investigated. In all three centres, the great majority of women felt positive towards the idea of a once-a-month pill which inhibited ovulation and >50% found a pill which inhibited or interfered with implantation an acceptable idea. Only 24% of women in Scotland were attracted to the idea of a pill which was taken only if menstruation was delayed by 1 or 2 days, that is a pill which would cause an abortion, while in contrast 58% of women in Slovenia and 80% in Romania thought that such a method of controlling fertility would be acceptable. Attitudes were not related to age, social class or marital status but were influenced by religious belief and in Scotland by a history of abortion. In countries where the availability of contraception is limited and abortion is common, women would seem to welcome another method of fertility regulation—even one which disrupts the very early stages of pregnancy.**

*Key words:* contraceptive pill/contraception/delayed menstruation

## Introduction

The most reliable currently available contraceptive methods depend for their efficacy on 'continuous' use. Innate human fertility in the absence of contraception is notoriously difficult to quantify (Short, 1976) but the chance of conception has been calculated from both demographic data (Sheps, 1965) and mathematical models (Tietze and Potter, 1962) to be at most ~28% per cycle. In order, then, to prevent perhaps one chance of conception every 3 months, women using 'continuous' methods of contraception do so for between 274 and 365 days each year.

The administration of the anti-progesterone RU486 at or shortly after the time of expected menses will induce menstrual-like bleeding and/or abortion in 85% of women (Van Look and Bygdeman, 1989). More recently it has been demonstrated that RU486 given to women shortly after the LH surge results in changes in endometrial histology and hormone receptor content compatible with the inhibition of implantation (Swahn *et al.*, 1990). With the advent of anti-hormones and anti-implantation agents, a pill which is effective in preventing pregnancy and yet which is taken only once each month may become a reality. In October 1991, Swahn and colleagues in a letter to *The Lancet* reported only one pregnancy in 80 cycles of use of RU486 taken only once a month as a contraceptive.

While a once-a-month pill may be a technical feasibility, an individual's choice of contraceptive method is influenced by a variety of factors including 'intensely felt individual values' (Mastroianni *et al.*, 1990). In this study, we have tried to determine whether a once-a-month pill is an attractive concept to three groups of women of reproductive age in three different countries where availability of contraception and availability and rates of abortion vary dramatically. In Scotland, contraception is widely available and free of charge and while abortion is legal and relatively easy to obtain, abortion rates are low. In Slovenia, the availability of contraception is more limited, abortion is legal and much more prevalent than in Scotland. In Romania contraceptive prevalence is extremely low and abortion, illegal for the past 25 years, was only legalized in 1990. We have also tried to establish whether the mechanism of action, and therefore the time when it may affect the potential pregnancy, significantly influenced the acceptability of such a method.

## Materials and methods

Twenty questions were devised to investigate the attitudes of women to the concept of a pill taken only once each month and to the possible modes of action of such a pill. Told that it was now technically possible to produce a pill which need be taken only once each month in order to prevent pregnancy (once-a-month pill) women were asked how, in principle, they felt about the idea. Details of previous contraceptive use and fear of side effects were recorded. The final question asked how women would feel about the idea of a pill which they would take only if their period was 2 to 3 days late (missed-period pill). It was made clear that no other method of contraception would be used; that the pill would work by dislodging an early embryo; and that they would probably only be in a position to need to use such a pill three or four times each year.

The questionnaire was administered during the second half of 1990 and the first half of 1991 to: (i) 400 women consecutively attending clinics at a large family planning centre in Edinburgh, Scotland (Dean Terrace); (ii) 400 women attending an outpatient gynaecology clinic (~40% attending for family planning) in Tirgu-Mures, Romania (Tirgu-Mures); and (iii) 100 women

attending a family planning clinic in Ljubljana, Slovenia (Ljubljana).

When the data from the women attending the family planning clinic in Edinburgh were analysed, it became clear that women who had children had slightly different attitudes than women who had not. It was therefore decided to involve a group of women who were pregnant at the time of completing the questionnaire and forms were distributed to women attending an antenatal clinic at the Simpson Memorial Maternity Pavilion (SMMP) in Edinburgh. Results were analysed after fifty questionnaires had been completed. Since there were no significant differences between the pregnant women and those attending the family planning clinic, no further questionnaires were distributed.

Every effort was made to simplify the questionnaire and to make it intelligible to all concerned. All questions were worded to allow a range of expression of opinions to be recorded and a five-point Likert scale was used. A pilot version of the questionnaire was given to 20 women at Dean Terrace and as a result of subsequent discussion with these women, modifications were made and a final version prepared. The questionnaire was translated locally into the Slovenian and Romanian languages. In Romania, many of the women have little or no understanding of the way in which contraceptive methods work and the questionnaire was administered by a trained interviewer who gave detailed explanations, with the aid of diagrams, where necessary. The questionnaire took 10–15 min to complete and no means of identification of the women was recorded. In Dean Terrace, no woman refused a questionnaire but 7% had no time to complete it: 88% of women answered all 20 questions. In Slovenia and Romania, all women asked to take part in the study did so.

Responses were coded and analysed in Edinburgh on an IBM PC using a Minitab Statistical program [Minitab data analysis software Version 5.1.1. (1986) 3081 Enterprise Drive, State College, PA 16801, USA] and in Tirgu-Mures, using Epi Info version 5.0. Significance values were obtained using the chi-square test for the two groups of 400 women (Dean Terrace and Tirgu-Mures) and Fishers exact tables for the SMMP and Ljubljana groups.

## Results

### *Characteristics of sample*

The demographic characteristics of the women taking part are shown in Table I. It is a little surprising that only 35% of the women in Tirgu-Mures had had an abortion when the rate in Romania is over twice that of the rate in Yugoslavia. However, abortion has only been legal in Romania since 1990; moreover it may be that many women are reluctant to admit to having had a pregnancy terminated before 1990.

Because it seemed likely that religious beliefs may influence women's attitudes towards contraception, we asked about both religious denomination and strength of belief. In the Slovenian sample, 54% of women were Roman Catholic compared with only small numbers in both the other centres. Most of the women in Scotland and 32% of the Romanian women were Protestant, 48% of the Romanians were Orthodox, the predominant denomination in the country and one which does not allow abortion. Despite the preponderance of Roman Catholics in Ljubljana, only 2% held strong religious beliefs and indeed 43% described themselves as atheist.

Of the women attending the family planning clinics in Edinburgh, a slightly but not significantly higher proportion than in the general population came from social classes I and II. We were unable to obtain any comparable details for women from the Eastern European countries; 85 of the 100 women questioned in Ljubljana were employed while 50% of the sample from Romania were described as 'factory workers' and 15% as 'intellectuals'.

### *Questionnaire replies*

#### *Attitudes to once-a-month and missed-period pills*

The percentage of women in each group who said that they felt positive or very positive and negative or very negative towards the idea of taking a once-a-month pill and towards the idea of taking a missed-period pill is shown in Table II. A small number of women in each centre said that they were neutral or did not know. Over 70% of women in all three centres were attracted to the idea of a once-a-month contraceptive pill. However, <25% of women in Edinburgh felt that they would be prepared to use no method but to take a pill which would disrupt a very early pregnancy; many in fact were actually negative about the concept. In contrast, over half of the sample in Ljubljana and 80% of the women in Tirgu-Mures felt positive towards this approach to the regulation of fertility.

#### *Mechanism of action*

In respect of the once-a-month pill (and before the missed-period pill had been mentioned), women were asked whether they would

**Table I.** Demographic characteristics of the women completing the questionnaire

| | Edinburgh (DT) | Tirgu-Mures | Ljubljana |
|---|---|---|---|
| *n* | 400 | 400 | 100 |
| Mean age ± SD | 28 ± 7 | 30 ± 7 | 34 ± 8 |
| Range (years) | 15–51 | 17–45 | 17–50 |
| % Married/cohabiting | 43 | 76 | 73 |
| % Never pregnant | 67 | 18 | 21 |
| % Ever had a baby | 17 | 73 | 75 |
| % Ever had an abortion | 18 | 35 | 55 |
| % Roman Catholic | 14 | 14 | 54 |
| % Holding strong religious beliefs | 15 | 20 | 2 |

**Table II.** Attitudes of the three groups of women to the idea of a once-a-month pill and to a missed-period pill

| | Edinburgh (DT) | Tirgu-Mures | Ljubljana |
|---|---|---|---|
| Once-a-month | | | |
| % Positive | 71.8 | 81.3 | 94.0 |
| % Negative | 9.5 | 4.1 | 3.0 |
| Missed-period | | | |
| % Positive | 24.2 | 80.0 | 58.0 |
| % Negative | 53.8 | 10.0 | 10.0 |

find such a pill more or less acceptable depending on whether it prevented ovulation, prevented implantation or acted after implantation. It is clear from Table III that women in all three countries do discriminate between modes of action and that all the women found a pill which inhibited ovulation significantly more acceptable than one which inhibited implantation. However, a method which works after implantation has occurred becomes unacceptable to the majority.

*Relationships between variables*

It was hypothesized that social characteristics and previous experience of contraception would influence attitudes. We predicted that older women with perhaps a lower frequency of exposure to the risk of pregnancy would find the concept of a once-a-month pill more attractive, while women who had undergone pregnancy termination would be more positive towards a 'missed-period pill. It was also hypothesized that women with strong religious beliefs and women who took into account the mode of action of a contraceptive when choosing a method may be more negative towards the idea of any pill which acted after ovulation had occurred. In fact neither age, social class, marital status, religion nor previous method of contraception used influenced women's attitudes to either of the proposed pill types in Scotland, Romania and Slovenia.

There were few significant correlations between the variables tested. Women who held strong religious beliefs were less positive ($P < 0.005$) about the idea of a once-a-month pill in both Scotland and in Romania although this relationship was only maintained among the Scottish women in respect of the missed-period pill. Women in Edinburgh who had been deterred in the past from using either an intrauterine contraceptive device or post-coital emergency contraception were significantly more negative about the concept of a once-a-month pill ($P < 0.01$) and about the concept of a missed-period pill ($P < 0.001$). Women who had ever had a pregnancy terminated were significantly more likely to be positive about a missed-period pill than the women who had never had an abortion ($P < 0.01$ in Edinburgh and $P < 0.05$ in Ljubljana); however a history of abortion had no effect on attitudes towards either pill in Romania. Women in Edinburgh who had children were less likely to be positive about the idea of a once-a-month pill than nulliparous women ($P < 0.05$).

Table III. Acceptability (% of women feeling positive) of a once-a-month pill according to mechanism of action

| | Prevent ovulation (%) | Prevent implantation (%) | Disrupt implantation (%) |
|---|---|---|---|
| Edinburgh (DT) | 90.4 | 64.1 | 15.7 |
| Ljubljana | 77.3 | 54.2 | 33.4 |
| Tirgu-Mures | 81.0 | 68.0 | 31.3 |

## Discussion

Since the introduction of the oral contraceptive pill some 30 years ago, there have been no major developments in the field of contraceptive research and no radically new methods of contraception have become available to the population at large. A once-a-month pill is an attractive concept to those of us working in the field of contraception. The currently available and more reliable methods of contraception have unwanted side-effects and risks which arise as a result of their 'continuous' use. Less total exposure to pharmacologically active contraceptive methods should reduce side-effects. Fecundability decreases significantly with age and frequency of intercourse (Leridon, 1979) and a once-a-month pill might be a particularly attractive proposition to older women, a large group for whom currently available methods may be particularly inappropriate.

It is clear from our study that the vast majority of women—whether they live in Scotland, Romania or Slovenia—are indeed attracted towards the idea of a once-a-month pill. Many women do appear to understand the implications of the mode of action of a method of contraception at least in terms of when during the reproductive process it has its effect. In the Dean Terrace sample, a small number of women said that they had been deterred from using both the intrauterine contraceptive device and post-coital contraception because of how the method worked. The same women were consistent in feeling significantly more negative than the rest of the women towards a pill which acted after implantation had occurred.

In all three countries, women preferred the idea of a pill which inhibited ovulation and for many the idea of using a method which acted after implantation would be unacceptable. It is hard to see how a once-a-month pill which inhibited ovulation could be developed since the inevitable desynchronization of the ovarian and endometrial cycles would not only result in an unacceptable bleeding patterns but would make the timing of pill-taking impossible to determine in all but the first cycle. Even the correct timing of a compound which acted early in the luteal phase prior to implantation would be difficult to achieve. However, a significant proportion of women would seem to find a pill which inhibited implantation an acceptable method of contraception, at least in principle.

Table IV. Contraceptive use among the sample and national abortion rates

| Contraceptive method ever used | Edinburgh | Ljubljana | Tirgu-Mures |
|---|---|---|---|
| Combined oral contraceptive % | 87.9 | 65.0 | 38.3 |
| Gestogen only pill % | 23.5 | 3.0 | 0.0 |
| Intrauterine contraceptive device % | 10.6 | 31.0 | 5.2 |
| Post-coital contraception % | 68.2 | 33.0 | 9.5 |
| Abortion rate/1000 women 15–44 years | 9.1 | 36.9 | 176.0 |

While most women in Scotland seemed to like the idea of a once-a-month pill, <25% found the idea of a missed-period pill acceptable and indeed the majority admitted to having negative feelings about it. In contrast, in Slovenia the majority, and in Romania, 80% of women asked found the idea of a missed-period pill attractive. In Edinburgh, women who had undergone a termination of pregnancy were more positive about the idea of both types of proposed pill. Contraceptive use and abortion rates (Table IV) vary widely between the three countries. In a country where a variety of contraceptive methods are easily available and are supplied free of charge and where the abortion rate is low, the idea of taking no precautions against pregnancy but waiting to act until a delay in menstruation has occurred is not widely acceptable. Opponents of abortion arguing against the so-called 'abortion pill' RU486 would have us believe that if abortion is made easier, more women will have abortions; our study would seem to suggest that this is not the case. Given the opportunity to induce menstruation after a missed period, most women in Edinburgh are not happy with the idea; whatever an individuals views on the rights or wrongs of abortion, this approach may seem somewhat cold-blooded. However, in societies where the availability of contraception is limited and where abortion is more common than childbirth, such a simple solution to controlling one's own fertility can only be an attractive one. In an unpublished study of contraceptive prevalence and attitudes towards abortion undertaken in Romania by Dr M.Horga, 96% of women asked felt that to use a method of contraception to prevent pregnancy was preferable to having an abortion. However, faced with the realities of an unwanted pregnancy, it would seem that women in Eastern Europe are prepared to renounce cultural, moral and religious beliefs and will accept almost anything. It is unlikely that this attitude is peculiar to Eastern Europe. The women in Edinburgh who had had an abortion were more positive about the idea of a pill which acted by disrupting an early pregnancy. Perhaps a woman who has never had to face an unwanted pregnancy can afford the luxury of discriminating between methods of contraception according to their mode of action. Attitudes may be modified by personal experience of an unplanned and unwanted pregnancy.

In conclusion, it is clear to us that most women in Europe would be interested in using a contraceptive pill which they need take only once each month. However, the acceptability of a pill which could be used for menstrual induction will vary between populations depending on the availability of methods which can be used to prevent a woman from becoming pregnant at all.

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# An international study on the acceptability of a once-a-month pill

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**Totals of 450 women attending family planning clinics in Hong Kong, Shanghai and Edinburgh, and 468 in Cape Town, completed a questionnaire designed to seek their views on a contraceptive pill which would be taken only once each month. At least two-thirds of the women in all centres liked the idea of a once-a-month pill. In Hong Kong, Cape Town and Edinburgh, women preferred a pill which inhibited ovulation to one which inhibited implantation, while in all centres a pill which worked after implantation (early menstrual inducer) was considered unacceptable by over half the women. A pill which was taken after a missed menstrual period was considered preferable in all centres, perhaps because it would not be used every month but rather only if pregnancy had occurred. No demographic characteristics, contraceptive experiences or beliefs were consistently correlated with attitudes towards a once-a-month pill, except that women who would not consider having an abortion were more likely to dislike a method that either prevented, or worked after, implantation. A once-a-month pill is now technically possible, although the major drawback is the need to determine when it should be taken. It is reassuring that many women from a variety of different cultures and with widely different experiences, would find this an attractive approach to contraception.**

*Key words:* contraception/contraceptive pill/mifepristone

## Introduction

Contraceptive prevalence is increasing globally: 56% of couples in developing countries and 73% in the developed countries of the world were using contraception in 1995. With population growth, however, the number of contraceptive users will need to increase by 50% by the year 2025 even to maintain prevalence at the current level (World Health Organization, 1998). In many countries, abortion rates are also rising. In developed countries, where contraception is easily available at minimal or no cost, roughly 50% of unwanted pregnancies arise from the failure of a method (usually less than perfect use), while 50% occur in women who have not used contraception (Griffiths, 1990; Yimin *et al.*, 1997). Despite an apparently wide choice of contraceptive methods, many couples are either unable to find one that suits them, or they persevere with a method with which they are somewhat dissatisfied. Despite reassuring data on safety, many women are concerned about the long-term exposure to steroid hormones, believing the daily ingestion of hormones to be 'unnatural' and unsafe (Oddens *et al.*, 1994). In 1991, a study was undertaken (Rimmer *et al.*, 1992) to assess the attitudes of women in three European countries (Scotland, Slovenia and Romania) to the concept of a pill which would be taken only once each month. Women were generally in favour, although the majority found the idea of a pill which acted after implantation to be unacceptable.

Since 1991, the development of a once-a-month pill has become feasible. In a pilot study (Gemzell-Danielsson *et al.*, 1993), it was reported that only one pregnancy occurred among 21 women who had taken a single dose of 200 mg mifepristone at midcycle during 124 cycles in which intercourse occurred during the fertile period.

In 1995, the UK Medical Research Council and Department for International Development jointly funded a programme of basic research in the development of new contraceptive methods in a network of centres in Shanghai and Hong Kong in China, Cape Town in South Africa, and Edinburgh in Scotland. Since one of the main areas of research was to be on the contraceptive effects of antigestagens, and recognizing that the acceptability of different methods of contraceptives varies widely in different cultural settings, it was decided to revisit the issue of the acceptability of a once-a-month pill in an international setting with widely disparate cultures and contraceptive practices.

## Materials and methods

The questionnaire used in the previous study (Rimmer *et al.*, 1992) was revised to investigate the attitudes of women towards a once-a-month pill, the possible mechanism of action, and practicalities for use. A pilot version of the questionnaire was administered to 25 women at the Edinburgh centre, and the final version was prepared as a result of discussions with these women. The questionnaires were administered by trained interviewers who gave detailed explanations, with the aid of diagrams where appropriate. The questionnaire took approximately 10–15 min to complete, and subjects remained anonymous. All questions were worded to allow a range of expression of opinions to be recorded, and a five-point Likert scale was used (Streiner and Norman, 1995). The questionnaire was administered to 450 women attending clinics at a large family planning (FP) clinic

in Edinburgh (The Dean Terrace Centre), to 450 women attending clinics of the Maternal and Child Health Centres in Hong Kong, and to 450 women attending clinics at the Shanghai Institute of Family Planning Technical Instruction. In Shanghai and Hong Kong, more than 97% of the respondents were Chinese, while in Edinburgh over 97% were of Caucasian origin. In Cape Town, a total of 468 women were interviewed at a variety of FP clinics selected to obtain equal numbers of the three main ethnic groups; black, coloured and white women (156 in each group). Within each setting all patients were invited to take part. The questionnaires were translated locally into Cantonese and Mandarin in Hong Kong and Shanghai respectively, and into Xhosa and Afrikaans for the Cape Town centre. During 1996, recruitment took place over 3 months in Edinburgh and Shanghai, and over 6 months in Hong Kong and Cape Town. Less than 10 women in Hong Kong and Shanghai declined to complete the questionnaire. In total, 162 women in Edinburgh, and 356 in Cape Town, declined to participate in the study. The over-riding reason was lack of time, but in Cape Town almost half the refusals were due to the patient speaking a different language from the interviewer.

Brief demographic data, details of previous contraceptive use and concerns about possible side effects of contraception were noted. The women were then advised that it was now technically possible to produce a pill to prevent pregnancy which need only be taken once monthly, and were asked—in principle—how they felt about the idea. It was then explained that such a pill may act in one of three ways: by preventing ovulation; by preventing implantation; or by disrupting implantation. The acceptability of each method was recorded. The final question addressed how women would feel towards a pill which they would take only if their period was 2–3 days late. It was made clear that this pill would act by dislodging an early embryo, and that they would probably need to take such a pill only three or four times each year.

### *Statistical methods*

The responses were coded and entered into databases at the individual centres and returned to Edinburgh for quality control checking and statistical analysis. The significance of associations between different variables was tested by $\chi^2$, Mann–Whitney, Kruskal–Wallis or Spearman rank correlation tests as appropriate. Multiple linear regression was used to test the effect on ordinal responses of several factors adjusted for one another, since the sample sizes were considered to be large enough to justify the normal approximations involved. The complete range of five-point Likert scales was used for significance testing, omitting those who did not know, but the percentages of women quoted as having 'positive' attitudes in the results refer to the combined numbers of those who were positive or very positive as a percentage of all women, including those who responded as 'don't know'.

## Results

### *Demographics of sample*

The demographic characteristics of the women who took part in the study are shown in Table I.

Women in Edinburgh and Cape Town were similar in age, marital status and smoking habits. Some 65% of women in Edinburgh had never been pregnant, compared with 48% in Cape Town. In Hong Kong and Shanghai, where family planning clinics are used almost exclusively by married women, over 90% of women were parous. A history of induced abortion was most common in Shanghai (68%) and least likely (at least to be admitted to) in Cape Town (1%), where at the time of the study abortion, although officially legal, was extremely difficult to obtain. There were major differences in past contraceptive use between the centres (Table II).

**Table I.** Demographic characteristics from each centre

| | Edinburgh | Cape Town | Hong Kong | Shanghai |
|---|---|---|---|---|
| No. of women | 450 | 468 | 450 | 450 |
| Mean ± SD age (years) | 26 ± 6 | 26 ± 5 | 34 ± 5 | 34 ± 8 |
| % Married/co-habiting | 41 | 40 | 99 | 92 |
| % Smoker | 28 | 30 | 6 | 2 |
| % Ever pregnant | 35 | 52 | 99 | 95 |
| % Ever abortion | 20 | 1 | 23 | 68 |
| % Strong religious beliefs | 11 | 54 | 3 | 9 |

**Table II.** Contraceptive use

| Contraceptive method ever used[a] | Edinburgh | Cape Town | Hong Kong | Shanghai |
|---|---|---|---|---|
| Combined oral contraceptive | 92 | 62 | 67 | 16 |
| Gestogen-only pill | 14 | 7 | 0.7 | 0.2 |
| Intrauterine contraceptive device | 9 | 5 | 22 | 64 |
| Injectables | 6 | 74 | 19 | 4 |
| Male condom | 93 | 44 | 82 | 40 |
| Post-coital contraceptive | 53 | 16 | 1 | 2 |
| Would consider changing method | 80 | 60 | 20 | 22 |

[a]Values are percentages.

**Table III.** Attitudes of the women (% positive) towards a once-a-month pill and a missed-period pill

| Type of pill | Edinburgh | Cape Town | Hong Kong | Shanghai |
|---|---|---|---|---|
| Once-a-month | 84 | 76 | 76 | 68 |
| Missed-period | 32 | 44 | 44 | 9 |

### *Attitudes towards the concept of a once-a-month pill*

In all centres more than two-thirds of women were in favour of the concept of a once-a-month pill (Table III). Womens' attitudes were independent of any of the demographic variables listed in Table I or, in Edinburgh, by past use or beliefs about contraception. In Hong Kong, women who had used the oral contraceptive pill in the past were more likely to be positive ($P < 0.05$), while in Shanghai women under 25 years of age ($P < 0.025$), and in Cape Town women over 25 ($P < 0.05$), were more likely to be positive to the concept.

### *Mechanism of action of a once-a-month pill*

Attitudes towards a once-a-month pill differed according to the mode of action (Table IV). There were no consistent factors which correlated with womens' preferences. In Shanghai, women who were better educated ($P < 0.025$) and older (≤30 years of age) ($P < 0.001$) were more likely to be positive about a pill which inhibited ovulation. In Cape Town, white women were more in favour of a pill which inhibited ovulation,

Table IV. Attitudes (% positive) towards a once-a-month pill according to its mode of action

| Mode of action | Edinburgh | Cape Town | Hong Kong | Shanghai |
|---|---|---|---|---|
| Prevent ovulation | 88 | 82 | 80 | 65 |
| Prevent implantation | 44 | 53 | 63 | 78 |
| Disrupt implantation | 20 | 33 | 49 | 7 |

regardless of their educational level ($P < 0.001$). Among black and coloured women there was a weaker correlation between educational achievement and preference for a pill which inhibited ovulation.

In Edinburgh, Cape Town and Hong Kong, acceptability of the method was much less if a pill was designed to inhibit implantation, with the greatest decline being in Edinburgh (Table IV). In contrast, in Shanghai women found a pill which inhibited implantation more acceptable (78% positive) than one which inhibited ovulation (65% positive). In Edinburgh and in Hong Kong, the difference in acceptability of the method according to whether it inhibited implantation or ovulation was influenced by knowledge or beliefs about the mechanism of action of existing methods commonly believed to inhibit implantation, such as the intrauterine device (IUD). Women in Hong Kong who found an IUD an acceptable method were more likely to be positive towards a pill which prevented implantation ($P < 0.001$), while in Edinburgh women who said they were unaffected by the way in which contraceptive methods worked were more likely to be positive ($P < 0.01$), and women who disapproved of emergency contraception were more likely to be negative ($P < 0.001$). In South Africa, a pill which inhibited implantation was more likely to be favoured by black women ($P < 0.05$) than by white or coloured women.

Acceptability declined in all centres, especially Shanghai, if the pill was said to dislodge an embryo which had already implanted (Table IV). Approval of this method was significantly related to approval of IUD use ($P < 0.001$ in Hong Kong and $P < 0.001$ in Cape Town) and neutrality about the mode of action of any method ($P < 0.01$) in Edinburgh. Attitudes towards abortion also correlated with attitudes towards the mode of action of a once-a-month pill which dislodged an embryo. In Hong Kong, women who would consider having an abortion if they had an unplanned pregnancy were more likely to be positive ($P < 0.001$), while women who would not consider an abortion were likely to have a negative attitude in Edinburgh ($P < 0.001$) and Cape Town ($P < 0.05$). In Shanghai, there was no effect of views on abortion. In Cape Town, white women (independently of their level of education) were least likely to approve of a method which dislodged an already implanted pregnancy ($P < 0.001$). Those coloured women who had received more years of education were also not in favour of this method ($P < 0.01$).

### *Missed-period pill*

Women were asked how they felt about using, as a regular method of contraception, a pill which was taken only if a period was missed. No other contraception would be used and (based on estimates of fecundability) women were informed that their period was likely to be late only three or four times a year. In Hong Kong and Cape Town, 44% of women were positive towards this idea (Table III). In Hong Kong, women were more positive if they were older ($P < 0.05$), less well educated ($P < 0.001$) and happy to use an IUD ($P < 0.001$). In Cape Town, in contrast, older women found the idea less acceptable ($P < 0.05$), but single women were more positive ($P < 0.05$), as were black women ($P < 0.01$). In Edinburgh, where only one-third of women found relying on an abortifacient acceptable, single women ($P < 0.01$) and those whose views were unaffected by the mechanism of action of any method ($P < 0.05$) were most likely to be positive. In Shanghai, where only 9% of women were positive, women who were separated were more likely to approve ($P < 0.05$) than those who were married or co-habiting.

## Discussion

Despite vastly different cultures, beliefs and experience with contraception, women in China, South Africa and Scotland do not differ substantially in their attitudes towards a pill which needs to be taken only once a month. In all centres more than two-thirds of the women who were asked thought that the idea was a good one. Attitudes towards how such a pill might work were also surprisingly similar. In all centres except Shanghai, most women would prefer to use a method of contraception which inhibited ovulation rather than one that inhibited implantation. This preference is likely to reflect personal views about the niceties of the stage in development when conception is interrupted. Indeed, women who expressed prejudices about the mechanism of action of a contraceptive method were consistent in the pattern of approval and disapproval. In Shanghai, hormonal contraception is not widely used (only 16% of women in this study had ever taken the oral contraceptive pill). It is commonly held that interference with the menstrual cycle leads to 'hormonal' side effects including obesity and hirsutism. It is possible that these beliefs explain the preference for a pill which inhibits implantation.

In all centres women expressed a strong dislike of a method which dislodged an already implanted embryo. Interestingly, on this issue the two Chinese centres—where abortion was most common—held the most extreme views, with over 90% of women in Shanghai disapproving of a pill acting after implantation compared with only 51% in Hong Kong. This observation is difficult to explain. While it may seem paradoxical that women might find a missed-period pill more acceptable than a pill which dislodged an embryo, it is possible that women might dislike a method which *intentionally* aimed to dislodge an embryo every month and may be more pragmatic or fatalistic about taking action after a pregnancy had actually occurred. These findings are in contrast to the suggestion that expected menses inducers (EMI) are more acceptable than missed menstrual inducers (MMI) (Harrison and Rosenfield, 1996). There was some consistency in womens' attitudes, as those who would not consider an abortion under any circumstances were most positive about contraception which

**Table V.** Percentages of women positive towards different methods of contraception in each centre according to whether they would or would not consider an abortion. Results from Shanghai are excluded as only one woman would not consider abortion

| | Attitude towards abortion | Edinburgh | Cape Town | Hong Kong |
|---|---|---|---|---|
| No. of women who would consider abortion | | 232 | 124 | 304 |
| No. of women who would not consider abortion | | 17 | 21 | 57 |
| Prevent ovulation (%) | + | 89 | 81 | 82 |
| | – | 94 | 29 | 78 |
| Prevent implantation (%) | + | 48 | 54 | 66 |
| | – | 35 | 24 | 61 |
| Disrupt implantation (%) | + | 26 | 37 | 55 |
| | – | 18 | 9 | 40 |
| Missed period (%) | + | 40 | 64 | 50 |
| | – | 29 | 86 | 39 |

**Table VI.** Differences among the three ethnic groups in Cape Town in responses to key questions

| | White (%) | Black (%) | Coloured (%) |
|---|---|---|---|
| Positive about a once-a-month pill | 74 | 85 | 68 |
| Positive about inhibiting implantation | 53 | 52 | 54 |
| Positive about dislodging an embryo | 36 | 23 | 37 |
| Positive about a missed-period pill | 56 | 35 | 40 |
| Held strong religious beliefs | 45 | 47 | 70 |
| Would consider abortion | 38 | 28 | 12 |

prevented ovulation, and were increasingly negative about intervening as the stage of pregnancy advanced (Table V).

Despite overall similarities, demographic differences might be expected to cause some minor variations in views. Women in the two Chinese centres, almost all of whom were married, were much less likely to consider changing their current method of contraception than women in Scotland or South Africa. A similar degree of satisfaction with their current method was described among men in Shanghai and Hong Kong who took part in a questionnaire study about male contraception (C.W.Martin *et al.*, personal communication). It is possible that contraceptive users in Shanghai have more faith in their doctors' advice than men and women in the West, where a tendency to question or actively disagree with figures in authority is more common.

Although different demographic characteristics correlated with different preferences in different cities, there was no one factor, or pattern of factors, which determined contraceptive choice. In general throughout their responses, women were consistent in the beliefs which they hold strongly, but even in South Africa—where ethnic differences might be expected to reveal marked contrasts in contraceptive preference—there was no clear pattern of response (Table VI). An individual's choice of contraceptive method is probably influenced by many factors, including past experience (of both contraception and reproductive events), technical or scientific knowledge, and beliefs about efficacy and side effects. Different methods suit different women at different times in their lives and given the choice, a once-a-month pill which acted before implantation would almost certainly be a well-used method of contraception. Our findings suggest that an EMI and MMI would probably be regarded as something of a last resort.

**Table VII.** Frequency of urine testing found acceptable (% of women)

| | Edinburgh | Cape Town | Hong Kong | Shanghai |
|---|---|---|---|---|
| Never | 20 | 8 | 19 | 31 |
| Once per month | 4 | 21 | 16 | 54 |
| Once per week | 31 | 49 | 30 | 11 |
| 5–6 days per month | 9 | 3 | 4 | 1 |
| Every day | 13 | 8 | 11 | 1 |

The results of this survey were not substantially different from those of the survey undertaken in 1991 which involved only European centres. Only in Edinburgh was the study repeated (in the same setting), and it is interesting to note that the percentage of women in favour of a once-a-month pill had increased from 72% in 1991 to 84% in 1996. There was also an increase in the number of women finding a missed-period pill an acceptable concept (24% in 1991 versus 32% in 1996). Perhaps this reflects a general liberalization of society's attitudes, and helps to explain the differences between Europe, Africa and Asia in the current survey.

If a once-a-month pill is to become available, it is likely that it will need to be taken at a precise time in the cycle. To do this, women will have to use a method of detecting ovulation, such as the measurement of luteinizing hormone (LH) in urine. It is likely that several tests will need to be done over a number of days, as accurate timing will be vital for the efficacy of the method. We asked the respondents whether they would be prepared to do this, and the results are shown in Table VII. In all centres <15% of women would be prepared to test their urine as frequently as would almost certainly be required (5–6 days/month) if ovulation were to be detected reliably. A method of contraception is already available in the UK which requires urine testing for up to 10 days each month (Bonnar *et al.*, 1999). The method—a fertility regulation monitor known as Persona (Unipath, Ltd., Bedford, MK44 3UP, UK)—is favoured by women who want to avoid using hormonal contraception. Given the option to use a method which exposes them to these drugs only 13 times a year, many more women may be prepared to endure the inconvenience of urine testing if the method were highly effective. With time, it may be possible to develop similar convenient monitors which measure indicators of ovulation in other, more acceptable fluids, such as saliva.

It is difficult to predict how many women would actually use a once-a-month pill were one to become available. Many other factors (e.g. related to compliance, cost, and provider acceptability) are involved in the process that leads to effective and safe use of a new contraceptive method. While it would be unwise to extrapolate precisely from the findings of this survey, the positive attitudes of so many women from such different cultures should nevertheless be reassuring to any pharmaceutical company interested in turning the concept into a reality.

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Contraception

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# Amenorrhea associated with contraception—an international study on acceptability

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**Abstract**

Surveys undertaken in the 1970s and 1980s suggested that amenorrhea was unacceptable to most women, especially in developing countries. More recent research suggests that increasing numbers of women in the developed world prefer to menstruate less often. In a questionnaire survey of 1001 women attending family-planning clinics and 290 contraceptive providers in China, South Africa, Nigeria and Scotland, only among black women in Africa did the majority like having periods. In all other groups, most women disliked periods, which were "inconvenient" and associated with menstrual problems. Given the choice, the majority of Nigerian women would prefer to bleed monthly. Elsewhere, women would opt to bleed only once every 3 months, or not at all. In all except the Chinese centers, the majority of women would be willing to try a contraceptive which induced amenorrhea. Providers tended to overestimate the importance of regular menstruation to their clients. This is an important observation for scientists and funding agencies involved in developing new methods of contraception. 

*Keywords:* Contraception; Amenorrhea; Acceptability

## 1. Introduction

When Pincus and colleagues developed the combined oral contraceptive pill, they purposely introduced a regimen which would confer a monthly withdrawal bleed because "these artificial menstrual cycles give assurance to the contraceptive user of 'normal' genital function" [1]. In contrast, the 3-monthly injectable method of contraception, depot medroxyprogesterone acetate (Depo Provera®), which became available a decade or more later, inhibits cyclical ovarian activity, doing away with menstrual periods in most users. For many years, amenorrhea was widely regarded as the price women had to pay for the clear advantages of the method in terms of efficacy and duration of action. When the levonorgestrel-releasing intrauterine device (Mirena®) came onto the market in the 1990s, the amenorrhea commonly associated with its use was heralded by the manufacturer, providers and users as a positive benefit of the method. There is no medical advantage to menstruation per se. On the contrary, the morbidity associated with menstruation is impressive. Menstrual dysfunction is one of the most common reasons for which a woman consults her general practitioner and in some countries up to 20% of women will undergo hysterectomy for excessive menstrual bleeding [2].

In the developed world, the gradual acceptance of amenorrhea associated with contraception has recently attracted interest. Surveys suggest that increasing numbers of

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women welcome methods which induce amenorrhea and indeed many manipulate their pill-taking to achieve it [3,4]. The debate has been taken a step further recently by the suggestion that whether to menstruate or not should be a matter of choice [5–7]. However, perceptions of menstruation vary according to culture and religion and women's attitudes to changes in bleeding patterns associated with contraceptive use vary widely. Research undertaken by the World Health Organization (WHO) published in 1981 suggested that most women (even in the UK, but particularly in the developing world) preferred to have a monthly bleed and were unwilling to use a method of contraception which induced amenorrhea [8]. These findings have strongly influenced not-for-profit agencies involved in contraceptive development, which have tended to shy away from exploring such methods. Since much of the research on attitudes to menstruation was carried out decades ago, we have undertaken a survey among women attending family-planning clinics, and among their providers. The study was designed to explore attitudes towards menstruation and willingness to use a method of contraception which induces amenorrhea.

## 2. Materials and methods

The survey was undertaken in two centers in the People's Republic of China (Shanghai and Hong Kong), two centers in Africa (Sagamu in Nigeria and Cape Town in South Africa), and in one center in Scotland (Edinburgh).

Two questionnaires were developed, one for women attending family-planning clinics (clients) and another for health professionals responsible for providing contraception (providers). Pilot versions of the relevant questionnaire were administered to 20 clients and five health-care providers at each center. Both questionnaires were modified according to the consensus of comments received and a revised version of the questionnaire for providers (which was changed quite extensively) was piloted before being finalized. The questionnaires were translated into local languages where appropriate and independent back-translation was performed to validate interpretation. The client questionnaire contained questions concerning gynecological history; methods of contraception ever used and reasons for stopping; clients/partners views towards menstruation; attitudes towards amenorrhea and, in particular, towards a method of contraception which may result in amenorrhea. The questionnaire for health-care providers probed factors which influenced their choice of contraception for a particular client and their perception of the importance to clients of menstruation during contraceptive use.

### 2.1. Subjects

In each center, clients were recruited from one or more family-planning clinics. In each clinic all clients were invited to participate and recruitment continued until 200 questionnaires had been completed. In Cape Town, to ensure that the views of all groups were well represented, clinics were selected to yield equal numbers of the three main ethnic groups (black, colored and white). Recruitment took place in all centers between December 2000 and June 2001. Following an explanation about the study and after obtaining verbal consent, the questionnaires were administered to the clients by trained interviewers and took approximately 5–10 min to complete. Questionnaires were posted (or hand-delivered) to health-care providers together with a return envelope. The number of refusals/nonreturns from each center was noted. All respondents (clients and health-care providers) remained anonymous. Ethical approval was obtained for this study by local ethics committees in each center.

### 2.2. Statistical analysis

Samples of 200 clients in each of the five centers allowed for the prevalence of moderately common attitudes to be estimated to within a standard error of 4% within centers, and gave high power to detect true differences in prevalence of the order of 15% between centers. The precision of estimation for attitudes of the health-care providers was lower, resulting in estimates with standard errors of the order of 8% within centers.

The responses to the questionnaires were coded and entered into databases at each of the centers and returned to Edinburgh for quality-control checking and statistical analysis. The significance of associations between binary or nominal variables were tested by chi-squared tests, with Yates' correction in the case of $2 \times 2$ tables, while appropriate nonparametric methods (Mann–Whitney, Kruskal–Wallis or Spearman rank correlation tests) were used for analyzing ordinal or quantitative variables.

## 3. Results

The questionnaire was administered to 200 clients in each of the five centers. In Edinburgh, Shanghai and Nigeria, no one refused to participate. In Hong Kong, 4 women and in Cape Town, 12 women declined to take part, mainly due to lack of time. At least 50 providers in each of the five centers were sent a questionnaire. All questionnaires were returned in Cape Town, Shanghai and Nigeria. In Hong Kong, 50 of 76 questionnaires were returned. In order to obtain 50 returned questionnaires from Scotland, a further 50 were distributed to the medical staff of the Sandyford Institute, Family Planning and Reproductive Health Center, in Glasgow. A total of 71 questionnaires were returned from 100 distributed to health-care providers in Edinburgh/Glasgow.

The demographic characteristics of the clients are illustrated in Table 1. As expected, there were significant differences between the various centers reflecting the different

Table 1
Demographic characteristics of clients from all centers[a]

| | ED (n = 200) | CT (n = 201) | HK (n = 200) | SH (n = 200) | NG (n = 200) | Significance of difference between centers |
|---|---|---|---|---|---|---|
| Age (years) (%) | | | | | | |
| 20–29 | 53 | 56 | 24 | 49 | 13 | $p < 0.001$ |
| 30–39 | 33 | 33 | 44 | 36 | 62 | |
| >40 | 11 | 7 | 31 | 16 | 26 | |
| Marital status (%) | | | | | | |
| Married/Cohabit | 49 | 33 | 84 | 81 | 99 | $p < 0.001$ |
| Single | 48 | 62 | 15 | 20 | | |
| Ethnic group (%) | | | | | | |
| B | – | 34 | – | – | 100 | |
| W | 97 | 33 | – | – | – | $p < 0.001$ |
| Ch | – | – | 92 | 99 | – | |
| C | – | 34 | – | – | – | |
| Religion (%) | | | | | | |
| Christian | 35 | 84 | 9 | 1 | 78 | $p < 0.001$ |
| Muslim | 0.5 | 9 | 0.5 | 1 | 23 | |
| Buddhist | – | 0.5 | 7 | 2 | – | |
| No religion | 64 | 6 | 74 | 96 | – | |
| No. of children (%) | | | | | | |
| 0 | 76 | 46 | 31 | 42 | 2 | $p < 0.001$ |
| 1 | 11 | 26 | 28 | 55 | 5 | |
| 2–3 | 13 | 25 | 41 | 4 | 36 | |
| ≥4 | 1 | 4 | 0.5 | – | 59 | |

[a] ED = Edinburgh; CT = Cape Town; HK = Hong Kong; SH = Shanghai; NG = Nigeria; B = black; W = white; Ch = Chinese; C = colored.

cultures. Clients in Edinburgh, Cape Town and Shanghai tended to be younger than those in the other two centers ($p < 0.001$) and more clients in Hong Kong, Shanghai and Nigeria were married. In Edinburgh most clients did not have children, whereas in Nigeria the majority of clients had four children or more. In contrast to the other two centers, the majority of clients in Edinburgh, Hong Kong and Shanghai stated that they had no religion.

The vast majority of women had regular menstrual cycles of average length (26–35 days) and menstrual bleeds of average duration (4–7 days). In no center did more than 4% of women have menstrual periods lasting more than 7 days. At least half of the women in every center reported their menstrual flow as being "normal." Two percent of women in Hong Kong, 10% in Edinburgh and 29% in Cape Town had no periods—most of them were using Depo Provera as their method of contraception. Of those women who stated that they experienced menstrual problems, the most common complaint in all centers was dysmenorrhoea (32–40%).

Table 2 illustrates the methods of contraception currently used by clients. The patterns of use were similar to those observed in previous studies from these centers [9,10]. In Edinburgh, the oral contraceptive pill was the most popular choice, while in Africa, injections were the most commonly used method (Depo Provera in South Africa and norethisterone enanthate in Nigeria). Nearly 40% of clients in Hong Kong and Shanghai used condoms.

Except for black women in the two African centers, more than half the women said they did not like having periods

Table 2
Current contraception (%)—clients[a]

| | ED | CT | HK | SH | NG |
|---|---|---|---|---|---|
| COC | 40 | 35 | 28 | 6 | 17 |
| POP | 7 | 5 | – | – | 0.5 |
| Condoms | 21 | 2 | 38 | 39 | 23 |
| IUCD | 9 | – | 12 | 17 | 27 |
| Inject/implant | 10 | 53 | 9 | 2 | 30 |
| None—at risk | 0.5 | 4 | 2 | 13 | – |
| None—no need | 4 | 2 | 4 | 6 | – |
| Planning pregnancy | 3 | – | 2 | 0.5 | – |

[a] ED = Edinburgh; CT = Cape Town; HK = Hong Kong; SH = Shanghai; NG = Nigeria; COC = combined oral contraceptive pill; POP = progesterone-only pill; IUCD = intrauterine contraceptive device.

Table 3
Attitudes and experience of clients towards contraception and amenorrhea[a]

| | ED | CT-B | CT-W | CT-C | HK | SH | NG | Significance of difference between centers |
|---|---|---|---|---|---|---|---|---|
| Do you like having periods? (%) | | | | | | | | |
| Yes | 26 | 75 | 35 | 42 | 50 | 33 | 81 | p<0.001 |
| No | 74 | 25 | 65 | 58 | 51 | 63 | 19 | |
| Don't know | – | – | – | – | – | 5 | – | |
| If you could choose, how often would you like to have a period? (%) | | | | | | | | |
| Monthly | 33 | 49 | 30 | 42 | 42 | 43 | 71 | p<0.001 |
| 3-monthly | 20 | 27 | 26 | 15 | 39 | 30 | 12 | |
| Never | 37 | 9 | 29 | 36 | 6 | 15 | 13 | |
| Have you used a contraceptive method which stopped periods? (%) | | | | | | | | |
| Yes | 23 | 60 | 32 | 37 | – | 1 | 20 | p<0.01 |
| No | 77 | 40 | 68 | 63 | 100 | 99 | 80 | |
| Provided your periods and your fertility returned to normal immediately after you stopped using it, would you consider a method of contraception which stopped your periods? (%) | | | | | | | | |
| Yes | 65 | 52 | 64 | 61 | 37 | 48 | 73 | |
| No | 25 | 41 | 26 | 33 | 32 | 35 | 24 | |
| Undecided | 11 | 7 | 11 | 6 | 32 | 18 | 4 | |

[a] ED = Edinburgh; CT-B = Cape Town (black); CT-W = Cape Town (white); CT-C = Cape Town (colored); HK = Hong Kong; SH = Shanghai; NG = Nigeria.

(Table 3). In South Africa, white or colored women were significantly more likely to say they disliked periods compared with black women ($p < 0.001$). The most common reason for not liking periods was because they were "inconvenient" (65–85%). In Edinburgh and Hong Kong, 33% and 13% of women, respectively, disliked periods because of associated menstrual problems. In contrast, 81% of women in Nigeria said they liked having periods, the most common reason cited was "to get rid of bad blood." They also liked having a period to reassure them that they were not pregnant. In all other centers, the most common reason for liking periods was because they were perceived as "natural."

Offered the choice of how often the clients would like to have a period, there were significant differences between centers (Table 3). More than one-third of all women in Edinburgh and colored women in Cape Town preferred never to menstruate, compared with fewer than 10% of women in Hong Kong and of black women in Cape Town. The proportion of women preferring a monthly bleed ranged from 30% among white women in Cape Town and 33% in Edinburgh, to 71% in Nigeria.

With the exception of Cape Town, the majority of clients in all centers had no experience with use of a method of contraception which stopped periods (Table 3). Within Cape Town, there were, however, differences between ethnic groups ($p = 0.002$). The majority (60%) of black clients had used a method of contraception which had stopped periods (Depo Provera) compared with fewer than one third of white women and 37% of colored women.

More than half the clients in Edinburgh, and all three ethnic groups in Cape Town, said that they would consider using a contraceptive method which resulted in temporary cessation of menstruation. In Shanghai and Hong Kong, more than one-third of women would be willing to use such a method. In Edinburgh, Cape Town and Shanghai, women who did not like having periods were more likely than those who did to consider a method of contraception which stopped periods ($p < 0.001$), but this was not the case in Hong Kong or Nigeria. Even amongst women in Nigeria, and black women in South Africa, most of whom had expressed a preference for having periods (Table 3), more than half of the women were favorable to the idea of using a method of contraception which would temporarily end menstruation.

The acceptability of a contraceptive which induced amenorrhea was unrelated to age, parity, education or religion except in Shanghai, where younger women (52%, $p = 0.015$) and women who wanted children ($p = 0.017$) tended to be more positive than those who did not. There was also no correlation between willingness to use this method and

Table 4
Demographic characteristics of providers from all centers

| | ED (n = 71) | CT (n = 50) | HK (n = 50) | SH (n = 50) | NG (n = 69) | Significance of difference between centers |
|---|---|---|---|---|---|---|
| Age (years) (%) | | | | | | p<0.01 |
| 20–29 | 17 | 13 | 20 | 26 | 10 | |
| 30–39 | 36 | 29 | 53 | 42 | 36 | |
| >40 | 47 | 58 | 27 | 32 | 54 | |
| Marital status (%) | | | | | | p<0.001 |
| Married/cohabit | 75 | 64 | 70 | 84 | 93 | |
| Single | 24 | 28 | 30 | 16 | 7 | |
| Ethnic group | | | | | | p<0.001 |
| B | – | 31 | – | – | 100 | |
| W | 92 | 35 | – | – | – | |
| Ch | – | – | 100 | 100 | – | |
| C | – | 35 | – | – | – | |
| Religion (%) | | | | | | p<0.001 |
| Christian | 71 | 80 | 34 | – | 86 | |
| Muslim | 3 | 8 | – | – | 14 | |
| Hindu | 3 | 2 | – | – | – | |
| No religion | 23 | – | 62 | 100 | – | |
| No. of children (%) | | | | | | p<0.001 |
| 0 | 41 | 24 | 46 | 30 | 7 | |
| 1 | 14 | 28 | 24 | 68 | 5 | |
| 2–3 | 43 | 40 | 30 | 2 | 58 | |
| ≥4 | 3 | 8 | – | – | 24 | |

ED = Edinburgh/Glasgow; CT = Cape Town; HK = Hong Kong; SH = Shanghai; NG = Nigeria; b = Black; w = White; Ch = Chinese; c = Colored.

how the client perceived her own menstrual period (i.e., normal, heavy or light).

There were significant differences between centers in the demographic characteristics of the health-care providers (Table 4). In all centers, over 70% of the providers were women and most were married. However, providers in Edinburgh/Glasgow, Cape Town and Nigeria were older than those in China ($p = 0.0013$) and the majority in Scotland and Hong Kong did not have children. In Scotland and in Hong Kong, providers were much more likely than their clients to describe their religion as Christian.

The attitudes of the health-care providers towards contraception and amenorrhea are illustrated in Table 5. Most providers in Nigeria, Shanghai and Hong Kong thought that it was important for women to menstruate while using contraception. In all the centers at least 75% thought their clients considered that menstruating whilst using contraception was important. Despite this, in all centers except Shanghai, more than half the providers would recommend a method which stopped menstruation.

## 4. Discussion

Regular monthly periods are a relatively recent phenomenon [11]. Until modern contraceptives became available, most women spent much of their lives pregnant or breastfeeding and, therefore, amenorrheic. Menses only returned briefly at weaning, which was rapidly followed by another pregnancy. The epidemic of menstrual cycles coincided with the demographic transition from developing to developed country status with low fertility rates. Faced with the inevitable inconvenience of repeated menstrual periods, women perhaps unsurprisingly adopted a positive attitude. Thus, periods were seen as "normal," a means of "getting rid of bad blood" and a sign of fertility. Amenorrhea could indicate ovarian failure and a sign of the end of reproductive potential at the menopause.

These ingrained cultural attitudes may explain the results of previous surveys. In a questionnaire survey of over 5000 women from 10 countries (Egypt, India, Indonesia, Jamaica, Korea, Mexico, Pakistan, Philippines, UK and Yugoslavia) undertaken in the late 1970s, the majority of women in all cultural groups were unwilling to accept a contraceptive which induced amenorrhea [8]. The size of the majority varied from 50% in Korea and 53% in the UK to 85% in India and 91% in Pakistan. Women in this survey were said to feel that amenorrhea was "unnatural" and that menstruation was "an outlet for bad blood." In a qualitative study undertaken in the early 1990s using focus discussion groups involving 576 women from seven countries (Cambodia, India, Mexico, Pakistan, Peru, South Africa and USA), a majority of women in every site strongly expressed their overall dissatisfaction with available methods of contraception [12]. The authors reported that, when directly asked, "women were largely dismayed by the prospect of a contraceptive method causing amenorrhea." Women were concerned about the negative health effects, fear of pregnancy

Table 5
Providers' attitudes towards contraception and amenorrhea

| | ED | CT-B | CT-W | CT-C | HK | SH | NG | Significance of difference between centers |
|---|---|---|---|---|---|---|---|---|
| Do you think it is important for women to have menstrual bleeding whilst using contraception? (%) | | | | | | | | $p < 0.001$ |
| Yes | 18 | 47 | 13 | 18 | 65 | 82 | 74 | |
| No | 82 | 53 | 88 | 82 | 35 | 18 | 26 | |
| How important does the client herself think it is to menstruate whilst using contraception? (%) | | | | | | | | |
| Very important | 18 | 60 | 25 | 24 | 26 | 28 | 79 | |
| Quite important | 74 | 33 | 56 | 65 | 72 | 62 | 17 | |
| Not important | 6 | 7 | 19 | 6 | 2 | 10 | 4 | |
| Would you recommend a method of contraception which stops bleeding? (%) | | | | | | | | |
| Yes | 92 | 71 | 100 | 77 | 66 | 36 | 52 | $p<0.001$ |
| No | 8 | 29 | | 24 | 34 | 64 | 48 | |

ED = Edinburgh/Glasgow; CT-B = Cape Town (black); CT-W = Cape Town (white); CT-C = Cape Town (colored); HK = Hong Kong; SH = Shanghai; NG = Nigeria.

and the difficulties that amenorrhea caused with keeping contraception secret from husbands.

In contrast, in our study, more than 50% of women in Edinburgh, Cape Town and Sagamu (Nigeria), and more than one-third of women in Hong Kong and Shanghai, would consider using a contraceptive method which induced amenorrhea. The proportion was high even among population subgroups of women (or cultures) in which the preference for having periods was widespread.

Why should our results be so different from those reported by the two earlier studies? Neither study described the source of the respondents but there is no indication that they were recruited from a health-care setting. Both sought only the views of married women with children. The women who took part in the questionnaire study [8] were markedly older than women participating in our study—in all but two cultural groups, at least one third were aged over 35 and in nine fewer than 15% were aged under 24. In the focus discussion groups [12], the mean age of participants was 32, and although the upper age limit was said to be 35, the reported range was much greater. In our own study, all the participants were attending family-planning clinics, many (76% in Edinburgh) had no children and more than 49% in Shanghai, Edinburgh and Cape Town were aged under 30. The differences could be due, therefore, to the type of women participating in the studies. However, in our survey, the women most likely to consider using a contraceptive which induced amenorrhea were the women from Nigeria (73%). Yet, these were the women who were most likely to like having periods (81%); most likely to choose to have a monthly withdrawal bleed (71%) and tended to view periods as a way of "getting rid of bad blood." They were also most likely to be married with children. So, in every respect, this group of women was more similar to those who participated in the two earlier studies. The study by Snow and colleagues [12] included 98 women from Cape Town and the WHO study [8] included a center in the UK. While the former study gave no absolute numbers, in the latter 53% of women from the UK were unwilling to accept a method of contraception which induced amenorrhea (compared with only 25% in Edinburgh in 2000). Perhaps a more likely explanation for the difference between the findings of our study and those of WHO and Snow is the effect of the passage of time. In a questionnaire survey of 178 pill users in Sydney, Australia, although 83% of women believed that a monthly bleed was necessary, 27% would choose to bleed every 3 months, 4% every 6 or 12 months, and 15% never [3]. Participants for this study were recruited from family-planning clinics or general practice, two thirds of the women were between 20 and 29 years, and almost half had never been married. Thus, these Australian women were more like our own respondents. Furthermore, this survey was done in the late 1980s when it is possible that women were becoming more accustomed to the concept that amenorrhea might have some benefits and that they do not *have* to bleed each month. The results may also reflect an increasing willingness of women to accept therapeutic interventions if the benefits are seen to be real.

In a more recent study undertaken in the Netherlands [4] published in 1999, the majority of women aged 15–34 preferred a bleeding frequency of less than once a month, and 26% of women aged 15–19 and 31% of those aged 25–34 would have preferred never to bleed. Given the opportunity to design their own pill regimen, one third of women aged 15–19 opted for a bleed once every 3 months and between 22% (aged 15–19) and 26% (aged 45–49) would design a regimen that induced amenorrhea.

Although neither the WHO survey [8] nor the Snow study [12] specifically asked women whether or not they liked having periods, WHO did ask women about physical discomfort and mood change and whether they would be willing to accept less bleeding. Although more than half of the women in every cultural group admitted to physical discomfort, and many to mood change in association with menses, in every center more than 60% (and in seven groups over 80%) of women were unwilling to accept less bleeding. In contrast, in 2000 in our study, only among black women (in both Cape Town and in Nigeria) did more than 50% of women say that they liked having periods. In Edinburgh, Cape Town and Shanghai, women who did not like having periods were more willing to try a contraceptive method which stopped periods.

There are data which testify to women's willingness to use the oral contraceptive pill (OC) to induce amenorrhea. More than 25 years ago, it was demonstrated in a Scottish study that the majority of women given the opportunity to use an OC continuously for 3 months found the regimen acceptable [13]. Ninety-one percent of the 107 women who completed the study (out of 195 women who started) refused to revert to the monthly regimen. Most of the women participating in similar trials of extended OC cycles in Australia [14], Sweden [15] and the USA [16] welcomed infrequent menses. Recognizing an increasing tendency for women to manipulate bleeds, a phase III trial of a combined oral contraceptive formulation taken continuously for 84 days followed by 7 days of placebo (Seasonale, Barr Laboratories) is underway in the USA. A similar study of continuous use of the combined contraceptive transdermal patch (ORTHO EVRA/EVRA, R.W. Johnson Pharmaceutical Research Institute, Raritan, NJ, USA) is also ongoing.

Anecdotal evidence from developed countries suggests that it is becoming increasingly common for women to manipulate their cycles to avoid a withdrawal bleed. In the study of Rutter and coworkers [3], 43% of women had used the pill to alter the timing of withdrawal bleeding for special occasions, holidays and weekends. Even women who are not using the OC look for ways to postpone menstruation. A review of prescribing patterns among general practitioners in Oxfordshire (UK) which showed clear peaks of prescribing every year for 4 years over the summer holidays, led the authors to describe norethisterone as a lifestyle drug [17].

Many factors influence a couple's choice of contraception. Providers, both through which methods they make available and accessible, and by their own attitudes and preferences, have a major influence. Few studies have looked at the influence of providers. Indeed, Snow [12] expressed regret at not probing further about the effect that providers have on determining women's preferences. In the Scottish study of tricycling the OC, while 82% of women who used the regimen welcomed the reduction in the number of periods, half of the doctors who worked in the participating clinic preferred to stick to the monthly regimen of prescribing [13]. Some 16 years later in the Australian study, 20 female doctors working at a Sydney teaching hospital answered the same questionnaire as the OC users [3]. The doctors were young (mean age: 24) but 40% were married. Sixty percent of them believed that a monthly bleed was necessary on the pill but more than half opted for less frequent bleeding episodes when given the choice of how often they personally would prefer to bleed and 30% chose never to bleed. In our own study, in every center except in white Cape Town, at least 90% of providers thought that *clients* felt that regular menses were either quite important or very important, while a much lower percentage of the clients themselves seemed to choose a monthly withdrawal bleed. In Nigeria, only 52% of providers, and in Shanghai only 36%, would recommend a contraceptive which induced amenorrhea, yet 73% of women in Nigeria and 48% of women in Shanghai said they would be prepared to try one. Thus, there was a tendency for providers' recommendations to correlate far more closely with their own views about menstruation than with the views of the women they treat. It is possible that the phenomenon of Westernization which is underway in major Chinese cities like Shanghai enhances the ability of clients to disagree with their providers and to adopt their own views of contraception as they become better informed. In black Africa, even in Cape Town, perhaps women have yet to become emancipated in this respect.

The acceptability of a method is often inferred from continuation rates. However, since most women using contraception are highly motivated to avoid pregnancy, they are prepared to tolerate side effects and the chosen method may be the "least worst alternative." Continuation rates may only be a reflection of the characteristics of the "best" method available rather than of those of a method which women would be truly happy to use were there more choice. Our study measures the hypothetical acceptability (or desirability) of one feature of a method of contraception—amenorrhea. Responses to a questionnaire survey may not be a true reflection of the number of women who would be prepared to try a method of contraception which induced amenorrhea if the method was actually available nor how many would continue to use it having tried it. However, our survey does suggest that attitudes may be changing. Scientists and funding agencies involved in developing new methods of contraception [18] and improving existing ones should be reassured that amenorrhea could be a popular option.

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# Potential impact of hormonal male contraception: cross-cultural implications for development of novel preparations

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**The prospect of a hormonal male contraceptive is no longer distant. Data on the potential impact of this improvement in contraceptive provision, however, is limited, particularly between different cultures. We have therefore carried out a multi-centre study to assess men's attitudes to proposed novel hormonal methods. Questionnaire-based structured interviews were administered to men in Edinburgh, Cape Town, Shanghai and Hong Kong. Approximately 450 men were interviewed in Edinburgh, Shanghai and Hong Kong, and a slightly larger group ($n$ = 493) in Cape Town to give samples ($n$ > 150) of black, coloured and white men. Knowledge of existing male and female methods of contraception was high in all centres and groups. The majority of men welcomed a new hormonal method of contraception, 44–83% stating that they would use a male contraceptive pill. Overall, a pill was more acceptable than an injectable form (most popularly given at 3–6 month intervals); long-acting implants were least so except in Shanghai. Familiarity with comparable female methods appeared to influence acceptability, for both oral and injectable methods. Hong Kong was the only centre where a male method (condom) was currently the most commonly used; men there appeared to rate the convenience of condoms highly while being least likely to think that they provided effective protection against pregnancy compared to other centres, and were least enthusiastic about novel male methods. The acceptability of potential male hormonal methods of contraception was high in some groups but showed wide variability, determining factors including cultural background and current contraceptive usage. These results suggest that the emerging emphasis that men should have greater involvement in family planning will be substantiated when appropriate contraceptive methods become available.**



*Key words:* acceptability/attitudes/cultural setting/knowledge/male contraception

## Introduction

Access to a wide range of effective methods of contraception is an important element of reproductive health. The development of new methods of contraception, such as the combined oral contraceptive pill in the 1960s and more recently medicated intrauterine devices (IUD) and long term implants, has been mainly female-directed. Despite this one-sided approach to contraceptive provision, a third of couples practising contraception world-wide use a male method (United Nations, 1994). Lack of demand for more advanced reversible male methods is frequently advocated as a reason for limiting the already meagre research effort in this field (Potts, 1996). The widespread usage of male methods, however, suggests that any lack of demand is more perceived than real, but there are limited data on this subject (Ringheim, 1993).

The prospect of a clinically available hormonal male contraceptive has been considerably advanced in recent years. The contraceptive efficacy of a prototype, testosterone-based, method has been demonstrated [World Health Organization (WHO), 1996]. Combinations of testosterone with a progestogen (Bebb *et al.*, 1996; Handelsman *et al.*, 1996; Meriggiola and Bremner, 1997) may show more rapid and consistent suppression of spermatogenesis, and long-acting testosterone preparations are becoming available (Behre *et al.*, 1995). Formulations may therefore include oral, injectable and implant preparations.

In view of this divergence between perceived need and actual usage, we have investigated men's attitudes to contraception. The progress in development of potential methods allows inclusion of likely specific formulations to address their potential impact, and the wide global variations in contraceptive usage necessitate that this be addressed in different cultures.

## Materials and methods

The participating centres in this study were Edinburgh, UK; Cape Town, South Africa; Shanghai and Hong Kong, People's Republic of China. A total of 1829 men (~450 per centre) was recruited between October 1995 and December 1996. The study group was recruited from (i) new or expectant fathers (exclusively new fathers in Shanghai); (ii) fire-fighters in Edinburgh, Hong Kong and Shanghai and army personnel in Cape Town; and (iii) men attending Blood Transfusion Services to donate blood. These groups were selected to achieve a sample population at different stages of their reproductive careers, and which would allow similar groups of men in the different centres

to be compared. Equal numbers of men were recruited from these three groups except in Cape Town: very few black men were recruited from Blood Transfusion; thus, to ensure approximately equal numbers from the coloured, black and white ethnic groups, additional men were recruited from the other two groups.

Data were collected through structured interviews using a questionnaire filled in by a trained interviewer. The questionnaire took ~30 min to complete. In each centre the questionnaire was translated from English to the appropriate local language by a fluent interpreter and checked by back-translation. Interviews were conducted in the subject's first language: English in Edinburgh, English, Afrikaans or Xhosa in Cape Town, Mandarin in Shanghai, and Cantonese in Hong Kong. In each centre, permission to conduct the study was granted from the local ethical committee. Informed consent was given by all subjects before interview.

The questionnaire aimed to assess the attitudes of men to currently available male methods of contraception and their opinion about oral, injectable and implant preparations which may become available in the future. The questionnaire therefore covered three main areas: (i) sociodemographic data, including religious beliefs; (ii) knowledge of contraception and current use; (iii) attitudes towards hormonal methods for men.

In Edinburgh, 80 men refused to complete the questionnaire, 34 refused in Hong Kong and 76 men in Cape Town, mainly due to lack of time. There were 45 refusals in Shanghai mainly because these men objected to the idea of a questionnaire about contraception.

### *Statistical methods*

All data were returned to Edinburgh for analysis. In general, completeness of data was high, typically 98–100%, with the exception of black Cape Town men for questions concerned with attitudes to contraceptive methods where completeness was ~93%. Associations between pairs of variables were tested by *t*-tests, $\chi^2$ or Spearman rank correlation tests as appropriate.

Multivariate linear regression was used to analyse the likelihood of men using novel hormonal male methods (5-point score ranging from 'definitely would' to 'definitely would not' use). Multivariate logistic regression was used to analyse men's first choice between condoms, a daily pill, injection or implant. For both linear and logistic regressions, the following factors were assessed for significance; age, having children (yes/no), wanting children in the future (yes/no), married/co-habiting (yes/no), and having a higher qualification (yes/no). Variables were selected for the model using forward selection with age given priority over the other variables since age was likely to affect other variables rather than vice versa. The analysis of men's first choice tested whether current contraceptive method influenced their preference.

Preliminary analysis demonstrated that there were only minor differences in attitudes between the three sources of recruitment (new and expectant fathers, blood donors and firemen/soldiers), thus these groups were combined.

## Results

### *Characteristics of study population*

In Cape Town, 493 men were interviewed (153 black, 171 white and 169 coloured), 450 men in Hong Kong and Shanghai and 436 in Edinburgh. Demographic details and reproductive status are shown in Table I. Men in Shanghai were older than in the other centres and the majority (70%) had completed their families. Only a small number of men declared no interest in having a family at any stage (2–6%).

### *Current contraceptive usage*

Table II shows the current contraceptives used by men or their partners in the four centres, excluding new or expectant fathers who would not have a current contraceptive requirement. There were marked differences ($P < 0.001$) between centres and between ethnic groups in Cape Town. The majority of men, other than black men, were using some form of contraception: 74% overall, 41% among black men. Female hormonal methods were the most widely used method of contraception in Edinburgh and all ethnic groups in Cape Town. Very few partners of Edinburgh men, white Cape Town men or Chinese men were using injectable methods. The IUD was the most common method in Shanghai, and uncommon in other centres. Only one couple in Shanghai was relying on female hormonal methods. Condoms were the most common method in Hong Kong, and the second or third most common method in other groups, accounting for 17–62% of current usage. Vasectomy was relatively common among white men in Cape Town and in Edinburgh, particularly in comparison with female sterilization, but was used very little in the other centres.

### *Knowledge of and attitudes to existing contraceptive methods*

Men were asked to give as many female and male contraceptive methods as they could think of, without prompting. Table III shows the proportions of men who recalled the major current female and male methods, and the proportions of men who had used those methods.

There was a highly significant difference ($P < 0.001$) between centres and ethnic groups with respect to knowledge of current male contraceptive methods. While knowledge was generally high, black men in Cape Town were unlikely to recall other than commonly used methods (condom, pill, and injection). Shanghai men had the greatest knowledge of methods of which they had no direct experience.

There were differences between centres in men's views on condoms for effectiveness ($P < 0.001$) and convenience ($P < 0.001$) but less so for decreasing sexual satisfaction ($P < 0.01$) (Table IV). Men in Edinburgh were most likely to regard condoms as effective but least likely to find them convenient to use whereas the opposite was found for Hong Kong men, where usage was highest: men there were least likely to think them effective for preventing pregnancy but most likely to regard them as convenient. This difference between Hong Kong and other centres also applied to men who were current condom users rather than just the group overall: only 72% of Hong Kong current users agreed that condoms were effective for preventing pregnancy compared to 92–95% of users in the other centres.

### *Attitudes to potential contraceptive methods*

Men were asked a series of questions about male methods which may be available in the future, i.e. a daily pill and injectable/implant contraceptives, and their answers were compared to their views on condoms (Table IV). In the introduction to the questions on proposed male methods, subjects were told that these methods would provide reliable contraception, would

**Table I.** Demographic details of participating centres

| | Edinburgh ($n$ = 436) | Cape Town | | | Hong Kong ($n$ = 450) | Shanghai ($n$ = 450) |
|---|---|---|---|---|---|---|
| | | Black ($n$ = 153) | Coloured ($n$ = 169) | White ($n$ = 171) | | |
| Ethnic origin | 99% white | 31% | 34% | 35% | 98% Chinese | 99% Chinese |
| Age (years) | | | | | | |
| Median | 31 | 27 | 31 | 29 | 32 | 40 |
| (range) | (18–52) | (19–57) | (18–52) | (19–60) | (16–59) | (21–59) |
| Marital status: | | | | | | |
| Married/cohabiting | 79 | 56 | 72 | 73 | 70 | 88 |
| Regular partner | 9 | 41 | 12 | 9 | 14 | 5 |
| No regular partner | 12 | 3 | 16 | 18 | 15 | 7 |
| Children: | | | | | | |
| Yes | 52 | 72 | 62 | 50 | 59 | 83 |
| Elective childless | 5 | 2 | 2 | 4 | 6 | 6 |
| Family not yet started | 42 | 26 | 35 | 45 | 34 | 12 |
| Family in progress | 19 | 46 | 25 | 17 | 29 | 13 |
| Family complete | 33 | 27 | 38 | 33 | 30 | 70 |

Values are median (range) for age, and percentages of respondents in each centre for other variables. Reproductive status was categorized as follows: elective childless, no children, none wanted; family not yet started, no children but would like some; family in progress, some children but want more; family complete, some children, no more wanted.

**Table II.** Current contraception (excluding new or expectant fathers)

| | Edinburgh ($n$ = 303) | Cape Town | | | Hong Kong ($n$ = 300) | Shanghai ($n$ = 298) |
|---|---|---|---|---|---|---|
| | | Black ($n$ = 79) | Coloured ($n$ = 119) | White ($n$ = 121) | | |
| Currently using contraception | 72 | 41 | 61 | 71 | 74 | 92 |
| Female hormonal method | | | | | | |
| Pill | 41 | 25 | 28 | 43 | 15 | 0 |
| Implant/Injection | 1 | 38 | 18 | 2 | 3 | 0 |
| Condom | 28 | 31 | 17 | 17 | 62 | 22 |
| Female sterilization | 7 | 3 | 13 | 13 | 9 | 3 |
| Vasectomy | 14 | 1 | 8 | 19 | 5 | 1 |
| IUD | 4 | 0 | 3 | 2 | 2 | 62 |
| Rhythm | 2 | 0 | 0 | 0 | 2 | 7 |
| Other | 4 | 3 | 8 | 2 | 1 | 5 |
| Are you happy with your current contraception? (Yes) | 71 | 97 | 80 | 88 | 83 | 92 |

Values are percentages of respondents in each centre. Data for those using particular methods of contraception are percentages of those currently using some form of contraception.
IUD = intrauterine device.

not carry significant risk of side-effects and would take 3–4 months to become effective. Questions were therefore designed to assess men's attitudes to these novel preparations separate from concerns about safety and efficacy although questions regarding these issues were included. Despite these reassurances, many men appeared to remain sceptical about the safety and efficacy of the proposed methods although there were large differences between centres. Thus there were differences between centres for perceived contraceptive efficacy, convenience, reduction in sexual satisfaction and reduction in masculinity ($P < 0.001$ in each case for both a male pill and an injectable contraceptive). This was particularly the case with Hong Kong men, of whom only 36% and 38% felt that a male pill and injection respectively would be effective at preventing pregnancy. As discussed above, however, Hong Kong men also had doubts as to the efficacy of condoms (only 60% believing them to be effective) despite the finding that they were the most widely used form of contraception in that centre and that 79% of condom users were happy with their current form of contraception.

Men had more positive attitudes to the convenience of novel male methods. The male pill was regarded as more convenient

**Table III.** Contraceptive knowledge and past usage

| | Edinburgh | Cape Town | | | Hong Kong | Shanghai |
|---|---|---|---|---|---|---|
| | | Black | Coloured | White | | |
| Existing methods recalled: | | | | | | |
| Rhythm (safe period) | 26 | 10 | 20 | 41 | 36 | 68 |
| Diaphragm/cap | 61 | 10 | 34 | 64 | 19 | 38 |
| Pill | 99 | 75 | 96 | 99 | 92 | 87 |
| IUD | 73 | 22 | 47 | 67 | 45 | 81 |
| Implant/injection | 25 | 75 | 86 | 71 | 56 | 47 |
| Sterilization | 22 | 35 | 70 | 72 | 48 | 66 |
| Female condom | 47 | 8 | 26 | 34 | 29 | 25 |
| Condom | 100 | 82 | 97 | 97 | 98 | 100 |
| Withdrawal | 24 | 29 | 62 | 68 | 26 | 83 |
| Vasectomy | 36 | 20 | 75 | 82 | 50 | 76 |
| Ever used: | | | | | | |
| Rhythm (safe period) | 5 | 3 | 9 | 15 | 17 | 31 |
| Diaphragm/cap | 11 | 1 | 2 | 6 | 0 | 4 |
| Pill | 78 | 16 | 49 | 66 | 24 | 14 |
| IUD | 9 | 2 | 10 | 8 | 2 | 50 |
| Implant/injection | 3 | 22 | 36 | 11 | 6 | 1 |
| Female sterilization | 3 | 1 | 6 | 8 | 4 | 3 |
| Female condom | 6 | 1 | 0 | 0 | 0 | 1 |
| Condom | 90 | 49 | 74 | 80 | 75 | 72 |
| Withdrawal | 14 | 17 | 39 | 46 | 11 | 44 |

Values are percentages of respondents in each centre. Subjects were asked to name as many contraceptive methods as they could, unprompted. They were then asked whether they had used any of the listed methods at any time.
IUD = intrauterine device.

to use than condoms in Edinburgh and in Cape Town. Men in the Chinese centres, however, regarded condoms as more convenient, particularly in Shanghai where only 38% of men thought a male pill would be convenient compared to 61% for condoms. Similar results were obtained when men were asked whether a male pill or injectable form would be inconvenient to obtain, with a minority (23–34%) of men in Edinburgh and Cape Town stating that an injectable form would be inconvenient, whereas 64% of men in Hong Kong and 46% in Shanghai felt it would be inconvenient.

Condoms were consistently regarded as decreasing sexual satisfaction in all centres (by 48–63% of men). While both a male pill and an injectable form were thought to be more satisfactory in this respect, 16–34% of black men in Cape Town and in the Chinese centres thought that a new hormonal pill or injection would decrease their sexual desire or masculinity. Men in all centres regarded condoms as safer for health reasons: this question was deliberately phrased in a non-specific manner to allow the subject to interpret it as they wished.

The preferred frequency of administration of potential injectable methods was investigated (Table IV). Proposed frequencies varied from monthly injections to implants lasting 3 years. The most popular intervals were 3 and 6 months except in Shanghai where 42% said they would prefer implants which lasted 3 years.

Men were asked whether they would use the proposed novel male methods (Table IV). Despite the above reservations, a majority of men said they would definitely or probably use a male pill (from 44% in Hong Kong to 83% among white Cape Town men). Responses to the same question regarding an injectable form were less positive in all groups, varying from 32% in Edinburgh and Hong Kong to 62% among white Cape Town men. There was a strong correlation ($r = 0.76$; $P < 0.001$) in all centres between men's willingness to use a pill and an injectable form, with nearly all men willing to use a male injection also willing to use a pill. Factors considered in Table IV were closely related to whether men thought they would use a novel male method. The strongest predictor for both pill and injectable methods was found to be whether the men thought their partner would wish them to use that method ($P < 0.001$ in all groups in each case with the sole exception of black Cape Town men for prediction of pill use, n.s.). Concern that novel methods would affect sexual desire was found to be a predictor of use of a male pill in Edinburgh, among black men in Cape Town and in Shanghai ($P < 0.01$ in each case) and for an injectable form in all groups ($P < 0.01$ except for black and white men in Cape Town, $P < 0.05$).

Relationships between demographic data and likely usage were investigated. In Edinburgh older men were more likely to consider a male pill ($P = 0.023$) whereas younger men in Hong Kong and white men in Cape Town were more likely to consider a male pill ($P < 0.001$ and $P = 0.026$ respectively). Edinburgh men were more likely to consider using an injectable contraceptive if they did not have a higher qualification ($P = 0.004$) whereas in Hong Kong men with a higher qualification ($P = 0.033$) were more likely to consider this method. Although there was no relationship between strength of religious belief (on a 5-point scale) and likelihood of using novel methods in any centre/group, all three ethnic groups in Cape Town were more likely to say that they would use a male pill if they

**Table IV.** Men's views on male methods

| Do you think that these methods: | Edinburgh | Cape Town | | | Hong Kong | Shanghai |
|---|---|---|---|---|---|---|
| | | Black | Coloured | White | | |
| Are effective for preventing pregnancy? | | | | | | |
| Condoms | 91 | 75 | 77 | 87 | 60 | 80 |
| Male pill | 74 | 65 | 85 | 91 | 36 | 52 |
| Injection | 69 | 74 | 79 | 88 | 38 | 46 |
| Are safe for health reasons? | | | | | | |
| Condoms | 82 | 76 | 73 | 73 | 82 | 75 |
| Male pill | 30 | 55 | 47 | 46 | 11 | 36 |
| Injection | 27 | 60 | 40 | 38 | 11 | 33 |
| Are convenient to use?[a] | | | | | | |
| Condoms | 59 | 71 | 76 | 74 | 79 | 61 |
| Male pill | 83 | 73 | 88 | 95 | 61 | 38 |
| Would be inconvenient to obtain?[a] | | | | | | |
| Male pill | 5 | 29 | 14 | 10 | 21 | 43 |
| Injection | 26 | 31 | 34 | 23 | 64 | 46 |
| Decrease sexual satisfaction/desire?[b] | | | | | | |
| Condoms | 59 | 48 | 55 | 63 | 52 | 60 |
| Male pill | 2 | 26 | 8 | 4 | 25 | 17 |
| Injection | 2 | 30 | 10 | 3 | 26 | 16 |
| Lessen your masculinity? | | | | | | |
| Male pill | 3 | 34 | 10 | 7 | 23 | 16 |
| Injection | 2 | 30 | 11 | 4 | 24 | 17 |
| Would you use this method? (definitely/probably) | | | | | | |
| Male pill | 66 | 55 | 66 | 83 | 44 | 50 |
| Injection | 32 | 48 | 55 | 62 | 32 | 35 |
| How often would you like an injectable/implant to be given? | | | | | | |
| Monthly | 8 | 18 | 7 | 15 | 8 | 6 |
| Every 3 months | 25 | 40 | 39 | 41 | 19 | 8 |
| Every 6 months | 32 | 15 | 21 | 29 | 24 | 19 |
| Once a year | 15 | 8 | 12 | 5 | 9 | 18 |
| Every 3 years | 16 | 7 | 9 | 7 | 10 | 42 |

[a]Different questions were asked to compare the self-administered methods (condom and pill), and methods requiring interaction with a service provider (pill and injection).
[b]'Satisfaction' when related to condoms, 'desire' when related to male pill and injection.
Values are percentages of respondents in each centre.

attended religious services ($P = 0.003$, $P = 0.022$, and $P = 0.040$ for black, coloured and white men respectively). There was no such relationship in the other centres.

### *Contraceptive preference*

The data in Table IV suggest that all groups would prefer to use a pill than an injectable form, particularly in Edinburgh where twice as many men would consider using a pill than a injection. The order of preference was tested more directly by asking men to rank condoms, a daily pill, a 3-monthly injection and a long-term implant (Table V). The proportion of men rating each method as first choice varied significantly between centres ($P < 0.001$ for all four methods). Condoms were first choice for over 60% of men in both Chinese centres, other methods being first choice for less than 20% of men. Condoms were also the first choice of 44% of black Cape Town men, but novel methods were first choice for men in Edinburgh and for coloured and white men in Cape Town. Edinburgh men showed a preference for a male pill (33% first choice), although this centre showed the most even distribution between methods. A 3-monthly injection was the most prevalent first choice for both coloured and white Cape Town men (41 and 39% respectively), with a pill being second choice in both groups. A 3-monthly injection was second most prevalent choice with black men. A longer acting implant was the least prevalent first choice among all groups except in Shanghai, but it was still only first choice with 17% of men in that centre.

Factors associated with contraceptive method of first choice were obtained by multivariate logistic regression. Condoms were more likely to be the choice of younger men in Edinburgh, white men in Cape Town, Hong Kong and Shanghai ($P < 0.05$ in each case). Black men in Cape Town were more likely to pick this option if they wanted (more) children in the future ($P < 0.01$). Current users of condoms were more likely to choose condoms except in Edinburgh and coloured men in Cape Town ($P < 0.01$ for black and white men in Cape Town, $P < 0.05$ for Hong Kong and Shanghai).

In Edinburgh, having a higher qualification was the only factor associated with ranking the male pill as the first choice ($P < 0.05$). For black and coloured men in Cape Town, none of the factors investigated show a significant correlation with choosing the pill. Current pill usage was predictive for this choice among white men in Cape Town and in Hong Kong ($P < 0.01$). This cannot be assessed in Shanghai as only one

Table V. Contraceptive preference

| | Edinburgh | Cape Town | | | Hong Kong | Shanghai |
|---|---|---|---|---|---|---|
| | | Black | Coloured | White | | |
| First choice | | | | | | |
| Condom | 28 | 44 | 19 | 16 | 68 | 61 |
| Pill | 33 | 19 | 29 | 30 | 12 | 8 |
| 3-monthly injection | 24 | 28 | 41 | 39 | 11 | 14 |
| Implant | 14 | 9 | 11 | 15 | 9 | 17 |
| Who decides which method of contraception to use? | | | | | | |
| You | 7 | 20 | 10 | 8 | 18 | 15 |
| Your partner | 13 | 26 | 18 | 11 | 15 | 16 |
| Both of you | 78 | 48 | 66 | 80 | 54 | 63 |
| Do you think that responsibility for contraception falls too much on women? (Yes) | 42 | 72 | 81 | 90 | 59 | 62 |
| Method characteristics: | | | | | | |
| Need for semen analysis | | | | | | |
| Agree[a] | 33 | 54 | 53 | 47 | 27 | 17 |
| Disagree[a] | 45 | 41 | 37 | 41 | 63 | 56 |
| 3–4 months to become effective | | | | | | |
| Agree[a] | 33 | 36 | 36 | 36 | 23 | 17 |
| Disagree[a] | 45 | 56 | 59 | 55 | 62 | 52 |

Values are percentages of respondents.
[a]Agree/disagree strongly or very strongly.

man indicated that his current method of contraception was the pill; however, men who were using methods other than the two main methods in that centre (condom and IUD) were more likely to choose the male pill.

An injectable form was more likely to be chosen by those men who were married or cohabiting in Edinburgh and among black and white Cape Town ($P < 0.05$ for Edinburgh and white men in Cape Town, $P < 0.01$ for black Cape Town men). This was not a predictive factor in Hong Kong, where current use of methods other than condoms was associated with men being more likely to pick this option. Not wanting any (more) children was a strong predictive factor among black Cape Town men ($P < 0.001$). No significant associations were found between any of the factors investigated and choosing this option among men in Shanghai.

Age was the main factor associated with first choice of an implant. Thus being older in Edinburgh, Hong Kong ($P < 0.01$) and Shanghai ($P < 0.05$) and having children in Edinburgh ($P < 0.01$) showed significant positive associations with this method. Current contraceptive usage was also a significant predictive factor for IUD users in Hong Kong and Shanghai ($P < 0.05$ and $P < 0.01$ respectively), using the pill in Edinburgh ($P < 0.01$) and among coloured Cape Town men ($P < 0.01$), and using injectable forms among black men in Cape Town ($P < 0.05$). These factors, however, did not show significant associations among white men in Cape Town.

### *Sharing responsibility*

The sharing of contraceptive decision-making was investigated. In all centres the majority of men reported that decisions regarding contraceptive usage were made jointly, varying from 54% in Hong Kong to 80% of white men in Cape Town (Table V). A majority of men in all centres except Edinburgh thought that the responsibility for contraception fell too much on women.

### *The need for semen analysis and delay in onset of efficacy*

It is likely that the use of male hormonal contraception will require analysis of one or more semen samples, therefore men were asked whether the necessity to supply a semen sample would be acceptable to them (Table V). There were significant differences between centres, men in Cape Town being most likely to find this acceptable and Chinese men in Shanghai and Hong Kong least likely ($P < 0.001$). Similar results were obtained when men were asked about the acceptability of a 3–4 month delay before the method became effective, with the exception of Cape Town where this was regarded as less acceptable than the need for semen analysis by all three ethnic groups.

## Discussion

Although a third of all couples world-wide rely on a male-dependent method of contraception (United Nations, 1994; Ringheim, 1996), there is an emerging emphasis that men should be involved in family planning (ICPD, 1994). The use of male methods also appears to be increasing in many developing countries (Drennam, 1998). Although many knowledge, attitudes and practice surveys relating to contraception have been carried out, few contain comparable data on men in different countries (Ezeh *et al.*, 1996; Drennam, 1998). This survey therefore sought to investigate men's attitudes to novel

hormonal forms of contraception which would provide effective male-dependent methods. While it is acknowledged that intention may not predict behaviour (Keller, 1979), the information obtained may be of value in the design of future products by biomedical scientists and the eventual introduction of a real method.

The recruitment of men from approximately the same three sources in the four different centres was designed to increase comparability between the centres. This design was adopted in preference to attempting to recruit a random sample from the local population. Blood donors and firemen/soldiers would not be expected to reflect the views of the wider population, but the third group, recent fathers, would be more likely to do so. Importantly, we did not find significant differences between the three recruitment groups in any of the centres, strengthening the validity of these data as representative of the population from which they are drawn. Although there will inevitably be differences between such diverse populations, the demographic details shown in Table I show considerable similarities in the composite variable of 'reproductive status', i.e. whether the men had or were planning children, or whose families were complete. Men in Shanghai, however, tended to be older, and consequently were more likely to have completed their families. The overall similarity in the responses of men in Hong Kong and Shanghai compared to the other two centres indicates that this had little impact, in agreement with the result of the detailed analysis showing the generally modest influence of reproductive status.

The major finding of this study is that the majority of men surveyed welcomed new hormonal methods of contraception even though they were mostly happy with their current method. Indeed 44–83% said that they would definitely or probably use a male pill. Attitudes to existing and novel methods, however, differed greatly between centres. Hong Kong was the only centre where a male-directed method (condom) was the main method currently used, and men in that centre were least keen on novel methods despite the high prevalence of reduction in sexual satisfaction with condoms (52%, similar to other centres) and low belief in their contraceptive efficacy (60%, lower than all other centres). Lack of belief in contraceptive efficacy also extended to novel hormonal methods despite being assured of this in the introduction to those sections of the interview. Condoms, however, were highly regarded for convenience. Conversely, men in Edinburgh were least likely to regard condoms as convenient although most likely to regard them as effective. These data therefore illustrate differences in factors influencing contraceptive usage in different societies. Thus the finding that a male pill was regarded as more convenient than condoms in Edinburgh and among all ethnic groups in Cape Town but not in Hong Kong or Shanghai may indicate large differences in potential usage. Similarly an injectable form was regarded as more inconvenient in Hong Kong and Shanghai than Edinburgh and Cape Town.

In addition to convenience, concern over interference with sexual functioning and partner's attitudes were strong predictors of potential use of novel methods. Both a male pill and an injectable form were perceived as having a much lower impact on sexual desire/satisfaction than condoms in all centres, particularly in Edinburgh and among coloured and white men in Cape Town. Similar differences between centres were apparent for concern as to whether novel methods would affect self-perceptions of 'masculinity'. However, compared to all other factors tested (Table IV), anticipated endorsement by the man's partner of usage of both oral and injectable novel methods was the most powerful predictor of potential usage.

Men's knowledge of both male and female existing contraceptive methods was generally high. The only exception was that knowledge among black men in Cape Town was largely restricted to past or present usage of methods. Conversely men in Shanghai had the widest knowledge. There are thus differences not only in knowledge and usage in different cultural settings, but also in the relationship between them. The high prevalence of men's knowledge of both male and female methods found here is consistent with an analysis of men's and women's knowledge and usage in 10, mostly African, countries (Hulton and Falkingham, 1996). In that study, usage of male methods was generally low, e.g. the highest rate of ever-use of condoms was 35% (in Ghana) compared to the lowest figure from the current data of 49% among black Cape Town men.

Relationships between age and willingness to use novel methods varied greatly between centres. Thus older men were more likely to use a male pill in Edinburgh, while this was more likely among younger men in Hong Kong who were also more likely to use an injectable form. Having a higher qualification also showed variable correlations, being less likely in Edinburgh men who would use an injectable form but more likely among such Hong Kong men. Age and level of education have frequently been found to have a significant influence on the acceptability of family planning methods in demographic and health surveys carried out in developing countries (Drennam, 1998). Reproductive status was generally not an important predictor of potential usage of a novel method in any centre. These findings demonstrate the importance of local and specific investigation of factors influencing uptake of family planning methods.

A second question to assess the potential impact of novel methods involved asking men to rank condoms and three novel methods: a daily pill, an injectable form lasting 3 months, and a long-acting implant. The most consistent finding was of the rejection of novel male methods in the two Chinese centres, with <15% of men ranking a pill or injection first choice. In contrast a significant proportion of men in Edinburgh and Cape Town would choose a pill, injection or implant demonstrating that, as in female contraception, user satisfaction is most likely to occur when a range of methods is available. Injectable methods appeared to be relatively more popular than a pill, in contrast to when men were directly asked whether they would use either method. This may be because in this section men were asked to rank four methods, none of which might have been acceptable. Current use and familiarity with comparable female methods appeared to affect acceptability, similarly to findings in the accompanying study of the acceptability of novel male methods to women (Glasier *et al.*, 2000): thus female pill use was highest in partners of Edinburgh and white Cape Town men, where potential male pill usage

was also highest. Similar relationships were also apparent for injectable method use, with both current female usage and proposed male usage highest in Cape Town. Current contraceptive usage was dominated by a single method in the two Chinese centres, over 60% using condoms in Hong Kong and IUD in Shanghai, and men in these centres were markedly less interested in novel male methods. Perhaps related to familiarity with the IUD, long-duration methods were relatively popular among Shanghai men: the lowest frequency of administration was most popular and an implant was rated as first choice by 17%.

One potentially valuable area of information from acceptability studies such as this is the identification of barriers to widespread usage of a method. Two relevant areas to novel male methods are the need for semen analysis to confirm azoo- or severe oligozoospermia, and the delay before adequate suppression of spermatogenesis is achieved. The need for semen analysis was regarded as acceptable by a small majority in Cape Town, but by only 17 and 27% in the two Chinese centres. These figures are lower than the proportions of men, even in the Chinese centres, who indicated that they would use a male pill or injection. As the question of semen analysis was raised towards the end of the questionnaire, it is possible that if it had been included earlier, it might have reduced the apparent acceptability of the methods. Men, however, were told that there would be a delay of 3 months before the methods would become effective in the introduction to the questions on each method. This was also regarded as a significant disadvantage to a novel method. It therefore appears that both a delay in onset of effectiveness and a need for semen samples would be significant barriers to the introduction of novel male methods of contraception. These are also key features of vasectomy, however, and do not preclude its widespread use.

Partners' attitudes to novel methods were a strong influence on acceptability to men, and the majority of men in all centres agreed that decisions about family planning should be taken jointly. This finding is in agreement with other studies in a variety of settings (Keith *et al.*, 1975; Davidson *et al.*, 1985; Grady et al., 1996; Drennam, 1998) and emphasizes the importance of our finding of very positive attitudes to hormonal male methods in a parallel study in women (Glasier *et al.*, 2000). The addition of further contraceptive options potentially adds to the total of contraceptive use, and the female partner's encouragement has been a major factor in men's willingness to volunteer for prototype male contraceptive trials (Ringheim, 1995). This finding, from participants in mostly Western urban locations of WHO studies, complements findings from developing countries of the importance of women as the principal sources of information about contraception for their partners (Ringheim, 1993).

While acceptability is recognized to be culture specific, failure to find new methods acceptable should not be attributed to cultural bias until access to the method is observed to be easy and appropriate education and information channels have been used to best effect (Ringheim, 1993). However, the present results suggest a major dichotomy between the acceptability of hormonal male methods in the two Chinese centres compared to the other centres. The similarity in the responses to this questionnaire between Hong Kong and Shanghai is despite major differences in current contraceptive usage as well as in economic/political terms, as this study was conducted shortly before Hong Kong became part of the People's Republic of China. The acceptability of novel methods among black Cape Town men was relatively high despite the finding that they had the lowest knowledge of current male methods, and is encouraging as to the potential widespread applicability of such methods.

Female-dependent methods have been the subject of considerable scientific advance, offering effective and male-independent contraception. Recent advances in the field of hormonal male contraception provide models for the characteristics of hypothetical preparations and although they remain experimental, the recent announcements of intent by major pharmaceutical companies adds credence to their successful development. The acceptability of potential male hormonal methods of contraception was generally high but showed significant variability between centres, determining factors including cultural background and current contraceptive usage. These results suggest that the current emphasis that men should have greater involvement in family planning will be substantiated when appropriate contraceptive methods are made available.

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# Would women trust their partners to use a male pill?

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**Despite a renewed interest in the development of hormonal contraceptives for men, many discussions about the potential acceptability of a 'male pill' end by speculating whether women would trust their partners to use the method reliably. To determine the views of women, we undertook a survey of 1894 women attending family planning clinics in Scotland (450), China (900) and South Africa (544). In all centres over 65% of women thought that the responsibility for contraception falls too much on women. More than 90% in South Africa and Scotland thought that a 'male pill' was a good idea, with Chinese women (71% in Hong Kong and 87% in Shanghai) only slightly less positive. Only 13% of the total sample did not think that hormonal male contraception was a good idea and only 36 women (2% of the total) said that they would not trust their partner to use it. 78% of Scottish women, 71% of Shanghai women, and 78% of white women and 40% of black and coloured women in Cape Town thought that they would use the method. This survey should dispel the myth that women would not trust their partners to use a 'male pill' reliably and illustrates the potential market for the method.**

*Key words:* hormonal contraception/male/women's attitudes

## Introduction

Increasing emphasis on the role of men in reproductive health has led to a renewed interest among scientists, funding agencies and policy makers, in the development of hormonal contraceptives for men [United Nations Family Planning Association (UNFPA), 1994; Harrison and Rosenfield, 1996]. Even in countries where the prevalence of male methods (condom and vasectomy) is low, the majority of men who have been surveyed claim to believe that they should take more responsibility for contraception [Ringheim, 1993; United Nations Development Programme (UNDP)/UNFPA/World Bank Special Programme of Research, 1999]. In surveys in which they have been specifically asked, a significant proportion of men from both developed and developing countries have expressed a willingness to use a hormonal method if and when it became available (Ringheim, 1993).

Recognizing that contraceptive failure has far greater personal consequences for the woman, many discussions about the need for, and acceptability of, hormonal contraception for men end by speculating whether women would trust their partners to use a method reliably (Ringheim, 1993; Potts, 1996). As part of a programme of research on the development of new contraceptive methods for men, we have undertaken two separate surveys in a number of different cultural settings. The attitudes of men towards a hypothetical hormonal contraceptive are to be published separately (Martin *et al.*, 2000). In this paper we report the findings of a survey designed to seek the views of sexually active women and specifically to ask whether they and their partner would use hormonal male contraception if it became available.

## Materials and methods

A total of 450 women aged 16–50 years attending family planning clinics for contraceptive advice and supplies was recruited from each of three centres in Edinburgh (UK), Shanghai and Hong Kong (People's Republic of China). In a fourth centre in Cape Town (South Africa), a larger group ($n$ = 544 women) was recruited in order to provide a representative sample of the three main ethnic groups, black ($n$ = 286), coloured ($n$ = 151) and white ($n$ = 107). In all centres patients were unselected, and consecutive attendees were invited to complete the questionnaire. In Hong Kong and Shanghai no one refused to participate, in Edinburgh 18 women and in Cape Town 16 women declined to complete the questionnaire, almost all for lack of time. Recruitment took place during 1996 over 3 months in Edinburgh, Shanghai and Hong Kong and over 7 months in Cape Town. A simple questionnaire, piloted in a family planning clinic in Edinburgh and translated into local languages, was administered by a trained interviewer. Questionnaires were completed non-attributably and sought information about demographic characteristics of the interviewees, satisfaction with current contraception and attitudes towards hormonal male contraception and its possible use. Local ethical committee approval was obtained in all four centres.

### *Statistical methods*

Descriptive analyses, including cross-tabulations of each question, by centre were performed first. Associations between pairs of categorical variables within centres were tested by $\chi^2$-test.

Table I. Demographic characteristics, current contraceptive use and response to the idea of hormonal contraception for men

| | Edinburgh | Cape Town ($n$ = 544) | | | Hong Kong | Shanghai |
|---|---|---|---|---|---|---|
| | ($n$ = 450) | Black ($n$ = 286) | Coloured ($n$ = 151) | White ($n$ = 107) | ($n$ = 450) | ($n$ = 450) |
| Mean age (years) | 27.6 | 30.0 | 29.2 | 28.0 | 31.3 | 30.9 |
| % ⩽20 | 18 | 15 | 14 | 4 | 11 | 2 |
| % >40 | 4 | 11 | 9 | 4 | 14 | 12 |
| % with higher qualification[a] | 42 | 13 | 32 | 69 | 3 | 19 |
| % married/ co-habiting | 49 | 35 | 61 | 56 | 71 | 96 |
| % with regular partner | 44 | 58 | 27 | 25 | 25 | 3 |
| % with children | 31 | 80 | 72 | 25 | 67 | 65 |
| Contraceptive method | | | | | | |
| % using oral contraception | 72 | 9 | 47 | 72 | 28 | 4 |
| % using injectable | 4 | 90 | 48 | 22 | 7 | 0 |
| % using IUD | 3 | 0 | 1 | 0 | 10 | 36 |
| % using condom | 15 | 0 | 1 | 4 | 40 | 34 |
| Other including NFP | 2 | 1 | 2 | 1 | 7 | 11 |
| None | 5 | 0 | 2 | 1 | 8 | 15 |
| % happy with method[b] | 64 | 93 | 84 | 79 | 59 | 44 |
| % unhappy[b] | 18 | 7 | 9 | 8 | 21 | 23 |
| Male contraception a good idea (%) | 94 | 93 | 91 | 97 | 71 | 87 |

[a]An additional 15% of women in Edinburgh and 5% in Hong Kong were students; in other centres no more than 1% were students.
[b]Only those women who recorded that they were currently using a method were asked this question.
IUD = intrauterine device; NFP = Natural Family Planning.

## Results

The demographic characteristics of the respondents, together with their current method of contraception, are shown in Table I. There were marked differences between the centres. For example 96% of women in Shanghai were married or cohabiting compared with only 49% in Edinburgh. The results of the survey have therefore been analysed on a within-centre basis.

Women who were using a method of contraception at the time of the survey were asked whether they were 'entirely happy' with that method (Table I) and if not, why not. Only 44% of women in Shanghai said that they were happy with their method, while in all other centres the majority of women were happy (59–93%). The condom was the method associated with the most dissatisfaction, with 48% of women in Edinburgh who used it (15% of the sample), 31% in Hong Kong (where 40% of women used the condom) and 23% in Shanghai (34% condom users) saying that they were unhappy. The main reasons for dissatisfaction were failure of a method (mentioned by 96 women, 58 of them condom users) and side-effects or long term risks (mentioned by 117 women, almost half of them in relation to oral contraceptives). A few women remarked on the inconvenience of having to remember to take the pill.

Women were told by the interviewer that it was now possible to produce a hormonal contraceptive for men which would not interfere with male sexual function and which, if used correctly, would be as effective as the female contraceptive pill. In all four centres the great majority of women thought that in principle this was a good idea (Table I). Asked why they thought so, over 84% of these women in each centre agreed that it would allow a more equal sharing of responsibility for contraception. In Shanghai 39% of them thought a hormonal method would be more effective than the male condom.

Women in Hong Kong were least likely to think that hormonal contraception for men was a good idea [131 women (29%) were either negative or unsure, Table I]. Fifty-eight women in Shanghai (13%) and only 37 in Cape Town (7%) and 28 in Edinburgh (6%) said they were unsure or did not think it a good idea. Chinese women were most likely to be concerned about associated side effects and health risks, whereas women in Edinburgh and Cape Town were more likely to say that they would not trust their partner to use a hormonal method. Between 18% (Hong Kong) and 67% (Shanghai) of these women said simply that they would not want to rely on a hormonal male method. Very few women, even in South Africa, were concerned about the spread of sexually transmitted infections.

Women who currently had a partner were asked whether, if a hormonal method for men was available, they would use it either now or in the future. They were also asked whether they thought their partner would use such a method and if so which route of administration he might prefer. Responses are shown in Table II. In Edinburgh, Cape Town (regardless of ethnic group) and Shanghai one-third or more of women with partners said that they would use a male hormonal method immediately, whereas in Hong Kong only 13% of women would do so. Asked if they would use the method at some time in the future, the percentages rose to over 70% of white women in Cape Town and women in Shanghai and Edinburgh.

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**Table II.** Responses of women with current partners to the idea of hormonal contraception for men. Values are percentages of women giving each response

| | Edinburgh | Cape Town ($n$ = 486) | | | Hong Kong | Shanghai |
|---|---|---|---|---|---|---|
| | ($n$ = 416) | Black ($n$ = 267) | Coloured ($n$ = 132) | White ($n$ = 87) | ($n$ = 432) | ($n$ = 447) |
| Use now | | | | | | |
| Yes | 38 | 33 | 36 | 45 | 13 | 33 |
| No | 23 | 29 | 30 | 21 | 44 | 25 |
| Use in the future | | | | | | |
| Yes | 78 | 43 | 46 | 78 | 14 | 71 |
| No | 5 | 22 | 18 | 6 | 30 | 6 |
| Would partner use it | | | | | | |
| Yes | 69 | 48 | 53 | 79 | 28 | 56 |
| No | 12 | 33 | 24 | 8 | 30 | 17 |
| Partner's choice of method | | | | | | |
| Daily pill | 55 | 21 | 17 | 23 | 23 | 24 |
| Monthly injection | 32 | 39 | 40 | 51 | 22 | 41 |
| Long-term implant | 6 | 2 | 11 | 16 | 13 | 23 |
| Don't know | 7 | 38 | 32 | 10 | 41 | 13 |

**Table III.** Reasons why women who did not think a male hormonal contraceptive 'a good idea' felt this way. Values are percentages of women giving each response

| | Edinburgh | Cape Town | | | Hong Kong | Shanghai |
|---|---|---|---|---|---|---|
| | ($n$ = 28) | Black ($n$ = 21) | Coloured ($n$ = 13) | White[a] ($n$ = 3) | ($n$ = 131) | ($n$ = 58) |
| Not trust partner | 50 | 38 | 46 | | 5 | 2 |
| Health risks | 21 | 0 | 23 | | 60 | 95 |
| Female responsibility if method fails | 21 | 29 | 15 | | 5 | 16 |
| Do not want to rely on a male method | 64 | 19 | 46 | | 18 | 67 |
| Infrequent intercourse | 4 | 5 | 23 | | 5 | 17 |
| Concern about STD | 11 | 0 | 15 | | 5 | 0 |

[a]Only three white women in Cape Town did not think male hormonal contraception a good idea, one because of health risks and infrequent intercourse and two because the responsibility for failure fell to the woman.
STD = sexually transmitted diseases.

The percentage for possible future use rose less markedly among black and coloured women in Cape Town while in Hong Kong women who would not use the method now would not use it in the future either. Women in Edinburgh and in Cape Town appeared confident that their partner would be as happy as they themselves were to use a hormonal male contraceptive at some time. In Shanghai, while 71% of respondents felt that they would like to use the method themselves at some time in the future, only 56% felt that their partner would want to. In contrast, in Hong Kong women seemed to feel that their partner would be more likely to want to use a male hormonal method than they themselves.

Fifty-five per cent of women in Edinburgh felt that their partner would be most comfortable taking a daily pill while a monthly injectable was the most popular preparation in Cape Town and Shanghai (Table II). A long-term implant was considered the best mode of administration by only a few women except in Shanghai where 23% thought that their partner would feel most comfortable with an implant.

## Discussion

The idea of hormonal contraception for men appears to be extremely popular. In all four centres, despite vastly differing cultures, beliefs and personal contraceptive experience, more than two-thirds of women thought it was a good idea. One-third or more of women who currently had a partner, in all centres except Hong Kong, said that they would use a hormonal male method now, and more than 70% of women in Shanghai and Edinburgh and white women in South Africa would use it in the future. Black and coloured women in South Africa were somewhat less likely than white women to think they they might use the method; nevertheless 40% of women with partners believed that they and their partner would use a hormonal male contraceptive at some time. Although they liked the idea, and although 28% of women in a relationship thought that their partners would use it, very few women in Hong Kong thought that they would ever rely on a hormonal method for men.

Despite what has been suggested, lack of trust really did

not seem to be much of an issue. Only 36 women (2% of the total sample) said that they would not trust their partner to use hormonal contraception (Table III). Only among black women in South Africa was lack of trust the most important reason for not liking the idea. Even in Hong Kong, where the idea of the method was least popular, only seven women said that they would not trust their partner to use it. In Shanghai the main reason for not liking the method was because of fear of side-effects. Hormonal methods are not widely used by women in China, with fear of side-effects accounting to some degree for their unpopularity. While we did not ask all women directly whether they would trust their partner to use a hormonal method we must assume that, if they foresaw that they would use such a method now or in the future, they would trust their partner.

Although there have been a number of studies in which men have been asked their views of hormonal methods for themselves (including our own in the same four settings (Martin *et al.*, 2000), we know of only two other studies which have sought the views of women. In a study undertaken in the late 1960s in the USA, Bardwick (Bardwick, 1973) interviewed 107 women, some attending a family planning clinic (FPC) and others students from the University of Michican. Women attending the FPC were planning to start using the combined oral contraceptive pill. The interviews were designed to predict psychological and psychosomatic responses to pill use. One question asked 'if there was a pill for men like the pill for women, who would you prefer to be responsible for contraception'? Seventy-two per cent of women said they wanted to be in control of contraception themselves, 16% preferred the man to take responsibility while only 12% felt that responsibility should be shared. Women were not asked anything more about male methods and were not asked specifically if they would use hormonal male contraception. A great deal has changed since the 1960s, however, and the responses contrast with a later study also carried out in the USA. In a randomized telephone survey of 1005 Americans (502 women) aged ⩾18 years, more than 70% of both men and women said that they thought men should play more of a role in using contraception. This study was undertaken by the Henry J.Kaiser Family Foundation (HJKFF, 1997) and was published in 1997. Forty-five per cent of women thought that men would take a 'male pill', fewer thought that they would use injectables or implants, while 36% of women in the survey doubted that men would use a hormonal method at all. The apparent lower popularity of a hormonal method for men in the USA compared with the only developed country in our survey (Scotland) may reflect the different populations surveyed since women in our study were currently using contraception, actively seeking advice or supplies and were asked whether they thought their partner, rather than just men in general, would use a method. On the whole many women have rather cynical views of men in general which do not reflect their views of individual men — especially their partner.

The choice of route of adminstration of a hormonal method for men varied between centres and probably reflects familiarity with the most popular delivery system for hormonal contraception for women in each centre — pills in Scotland and Hong Kong, injections in South Africa. In Shanghai, where hormonal contraception is not very widely used, an injectable method was favoured.

Despite the widespread belief that women would not want a 'male pill' because they would not trust their partners to use it reliably, our study suggests that a hormonal method for men would be extremely popular and that many women, regardless of culture, would trust their partners to use it. Presently a male pill is likely to be less popular in the Far East than in the West but, despite what many might predict, it may certainly have an important role in Africa. More choices of contraceptive methods for men will allow increasing numbers of men in all countries to accept more responsibility for reproductive health, and certainly their womenfolk are keen that they should do so. Approval of, and intention to use, a hypothetical method of contraception is unlikely to be accurate in predicting behaviour when such a method becomes available. However, even if the number of potential users is overestimated by a factor of 10, a hormonal method for men would still represent a greater share of the market than contraception implants, injectables or the progestogen-only pill in the UK, and no one would dream of questioning their important role in contraceptive choice.

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# Noncompliance among a group of women using a novel method of contraception

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**Objective:** To compare the incidence of noncompliance measured objectively by a home use fertility monitor with the traditional self-reported incidence of compliance in a study of a new method of contraception.

**Design:** Prospective cohort study.

**Setting:** A large family planning clinic in Edinburgh.

**Patient(s):** Thirty-two healthy women who took part in a trial assessing the efficacy of a novel method of contraception involving accurately timed administration of a single dose of mifepristone.

**Intervention(s):** Mifepristone was administered orally and a blood sample was collected on the same day.

**Main Outcome Measure(s):** Percentage of missed tests detected by the monitor against the self-reported percentage during the critical period.

**Result(s):** Women failed to perform 24.2% (95% confidence interval, 16.5–31.5) of the tests in the 162 cycles analyzed. They missed tests at an absolutely vital time for contraceptive efficacy in 42% of cycles according to the monitor while admitting to missing tests in 14.8%. Poor compliance was associated with younger women, those who discontinued the study before completion, and cycles in which women were not relying on the contraceptive method.

**Conclusion(s):** The use of microelectronic monitoring systems may improve our understanding of the extent of patient noncompliance, providing objective information that no other monitoring technique can produce. This understanding provides the opportunity to make the optimum use of potentially effective treatments while validating research evidence. (Fertil Steril® 2001;76:1196–1201. ©2001 by American Society for Reproductive Medicine.)

**Key Words:** Compliance, contraceptive research, home-use fertility monitor, mifepristone

Since the first woman on earth chose to contradict the instructions of her Provider in the Garden of Eden, expecting her descendants to comply perfectly with a contraceptive regimen may seem rather unrealistic. However, noncompliance with a particular contraceptive method is linked with an increased risk of unintended pregnancy (1). Conventionally, it has been assumed that the users of contraception are highly motivated because the consequence of noncompliance —pregnancy—is so obvious, and so significant. Studies involving organ transplant recipients have shown, however, that no consequence of poor compliance is severe enough—not even the rejection of a transplanted kidney—for all patients to reliably follow their prescribed regimen (2).

Poor compliance—in both clinical practice and research—is associated with a number of factors. Though several patient characteristics (e.g., age, education, socioeconomic background) (3–5), characteristics of the treatment regimen (e.g., frequency of dosing, side effects) (6–8), and outcome characteristics (e.g., treatment of incurable or terminal illnesses) (9) have been associated with nonadherent behavior, there are no reliable and universally applicable predictors of noncompliance. In addition, there is no gold-standard measurement for patient compliance (10).

Prevalence of noncompliance ranges from 0–96.6% in oral contraceptive pill users (11–13). Although extremely common, there is a dearth of information available on patient noncompliance with the use of different contraceptive methods. What data exist commonly come from self-reporting. When undetected, poor compliance can invalidate results of efficacy

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studies (14, 15), yet it is commonly overlooked in clinical research (16).

We observed behavior of 32 women who took part in a trial assessing the efficacy of a novel method of contraception (17). The women took 200 mg of mifepristone 2 days after the midcycle LH surge (measured in urine) as a once-a-month contraceptive pill. Mistimed administration of mifepristone can disrupt the menstrual cycle and can also leave the women at risk of conception. A home use fertility monitor that could store data on daily testing events was used to time the administration of mifepristone. Although it made minimal demands on the users, the method provided objective, long-term data on their routines. Because investigators saw participants once each cycle throughout the study, we were able to compare the results of this method with the traditional self-reported incidence of compliance.

## MATERIALS AND METHODS

Data were collected during a study assessing the feasibility of administering mifepristone as a once-a-month contraceptive pill, and detailed study methodology has been reported elsewhere (17). Thirty-two sexually active women (age range, 18–39 years) were enrolled from a large family-planning clinic in Edinburgh. (The mean body mass index was 24 ± 4.3, and 66% were nonsmokers.) All subjects gave written informed consent to participate, and the Lothian Research Ethics Committee approved the study. Data were collected from a total of 178 cycles, with each subject contributing between one and eight cycles. It was not possible to retrieve compliance data from the monitors in 28 of the study cycles because of infrequent downloading from the monitor and lost or broken devices.

The study started on day 1 of the menstrual period after screening and lasted for up to eight consecutive menstrual cycles. The subjects were relying on once-a-month treatment with mifepristone as their sole method of contraception during 150 of the cycles analyzed. In addition, it was possible to retrieve data from a further 12 cycles during the study suspension period, during which women did not rely on our method for contraception but only used the monitor. During the cycles in which mifepristone was administered, the timing of mifepristone depended on detection of the LH surge, which in turn depended on compliance with daily urine testing.

### Procedure

All subjects were provided with a home use fertility monitor (Unipath, Bedford, UK). The system comprises a hand-held monitor and disposable dual-assay urine test sticks and is used to detect simultaneously LH and estrone-3-glucuronide levels in early-morning urine. The system delineates three levels of fertility (low, high, and peak fertility) according to the optical signal changes detected. At the start of each menses, the subjects pressed the *m* button on their monitors to initiate that cycle of use at a time suitable for testing the first urine of the day.

For the rest of the month, the subjects were required to consult the monitor display each morning (3 hours on either side of the time when the *m* button was set) to determine whether they needed to perform a test that day. Without this 6-hour time window, the system would not accept a test. The monitor requests one test every day for up to a total of 10 or 20 tests, depending on the length of the woman's cycle and the timing of her LH surge. Embedded software within the monitor collects, analyzes, and stores data for several months.

The correct way to use the monitor (including the importance of the testing window) was demonstrated to all subjects at the time of recruitment, and written information was given. Subjects were advised to contact the investigator immediately if they were not able to perform a test during a critical period. The investigator was available by telephone 7 days a week.

In each cycle, subjects were reviewed by the investigator monthly, on day LH+2. A sample of venous blood was collected before taking the tablet of 200 mg mifepristone and was later used for the analysis of progesterone. The information collected by the monitor was later analyzed using special computer software. The estimated day of LH peak for each month was calculated based on information from all the previous cycles monitored. If an LH surge was not detected either within 3 days after the anticipated day of LH peak or by day 19 of the cycle, a blood sample was taken for rapid serum progesterone assay, and the information from the monitor was downloaded. Mifepristone was administered only if the woman was at risk of pregnancy (i.e., had been sexually active) and if the progesterone level was >5nmol/L.

All subjects kept a menstrual record card, recording all vaginal bleeding experienced during the study and the days on which they had sexual intercourse. They also marked the day of the LH surge as identified by the device and the day of taking the study medication.

The following definitions were created for the purpose of the study. The period of time between the calculated earliest day an LH peak was likely to occur (based on the usual cycle length and the day of the LH surge in previous cycles) and the day of the actual LH surge in each cycle was defined as the *critical period* for each patient. The *fertile period* of the cycle was defined as 3 days before until 2 days after the urinary LH surge (LH−3 to LH+2). *Exposure cycles* were cycles in which women reported having sexual intercourse at least once during the fertile period. *Noncompliance* was defined as a urine test that was requested by the monitor but missed.

### Statistical Methods

Some of the compliance data were summarized for descriptive purposes using numbers of cycles or tests as de-

nominators. However, statistical inference was carried out on data aggregated to patient level, to take account of possible heterogeneity in behavior among patients that might have invalidated analyses using data from individual cycles or tests. Thus, percentages of tests missed were calculated for each patient, and these were tested for association with demographic data using Pearson correlations. Testing was done on data aggregated to patient level. Thus, for example, correlating each patient's age with the percentage compliance over all her cycles tested the association between age and compliance. Similarly, percentages of tests missed at different stages of the cycle, and when on and off the treatment regime, were compared by paired *t*-tests. A two-sample *t*-test was also used to compare the percentage of tests missed in patients who dropped out and those who did not.

## RESULTS

One hundred sixty-two cycles were analyzed, of which 150 were study cycles. Data collected during the 12 cycles during which subjects were using a barrier method throughout the cycle and did not receive mifepristone were analyzed separately.

In total, 2,013 tests were requested by the monitor during the 162 cycles analyzed (12.4 tests per cycle, 95% confidence interval [CI], 11.8–13.0), and 494 were missed (24.2%; 95% CI, 16.5–31.5). On average, three tests (95% CI, 2.4–3.6) per cycle were missed.

### Compliance During the Intention-to-Treat Cycles

During the 150 cycles in which women were relying on the study method as their only contraception, a total of 1,816 tests was requested by the monitor, and 411 tests were missed (22.6%; 95% CI, 15.2–30.1).

### Compliance Before and After Identifying the Peak

In the days before the women knew an LH surge had occurred, 23% of the requested tests were missed (95% CI, 16–30; 260 of 1,160). Women were not more likely to miss tests before the LH surge than after it ($t = 0.57$, NS).

### Concordance of Monitor Data With the Self-Reported Data

In 68 cycles (42%), women failed to test at all on a day of the cycle, which was critical to the accurate detection of an LH surge. In 27 of these cycles, the monitor did not detect an LH peak. In the remaining 41 cycles, despite critical tests being missed, the monitor did detect an LH peak. Women admitted to not performing tests in 24 cycles (14.8%). In the other 44 cycles, women did not report missed tests and only admitted to it once the investigator showed the downloaded monitor data to them.

Some women actively fabricated the information that they reported to the investigator. In one of these cycles, when contacted, a woman declared detecting an LH peak on a day (day 13 of the cycle) when she had not performed a test at all. Another woman performed the tests correctly and identified an LH peak on day 13 but forgot to inform the investigator and failed to obtain the mifepristone tablet as per protocol. When contacted on day 19 of the same cycle, she claimed that the monitor had not detected an LH peak.

### Compliance During the Critical Days

Noncompliance with urine testing as monitored by the system was significantly lower during the critical period (15.6%; 95% CI, 9.5–21.7) when compared with during the noncritical days (27.5%; 95% CI, 17.9–37; paired *t*-test, $t = 3.64$, $P<.01$). The self-reported percentage of missed tests during the critical period was 2.7% (95% CI, 1.0–4.3), which was significantly lower than that detected by the monitor ($t = 4.48$, $P<.001$).

### Compliance During the Study Suspension Interval

After a pregnancy that occurred because of a failure in detecting a LH peak, the study was suspended for a month. However, some women continued to use the monitor only, while using a barrier method for contraception. Therefore, it was possible to retrieve data from the monitors for 12 cycles in which the women were not using our method as their contraceptive.

In six of these 12 cycles, the monitor was not able to identify an LH peak because of its imperfect use. During this period, a significantly high percentage of tests (41.2%; 95% CI, 22.4–60.0) were missed when compared with the study cycles (22.6%; 95% CI, 15.2–30.1; $t = 2.9$, $P=.015$).

### Compliance and Sexual Activity

There was no correlation between the frequency of sexual intercourse per cycle and the number of missed tests per cycle (correlation coefficient was 0.01). The percentage of missed tests were compared between the exposure and nonexposure cycles in 12 women who had at least one exposed and one unexposed cycle. There was no significant difference (paired *t*-test, $t = 0.06$, NS; 95% C.I for differences between exposed and unexposed, −8.3 to +7.8) in compliance during exposed and nonexposed cycles.

### Demographic Features and Compliance

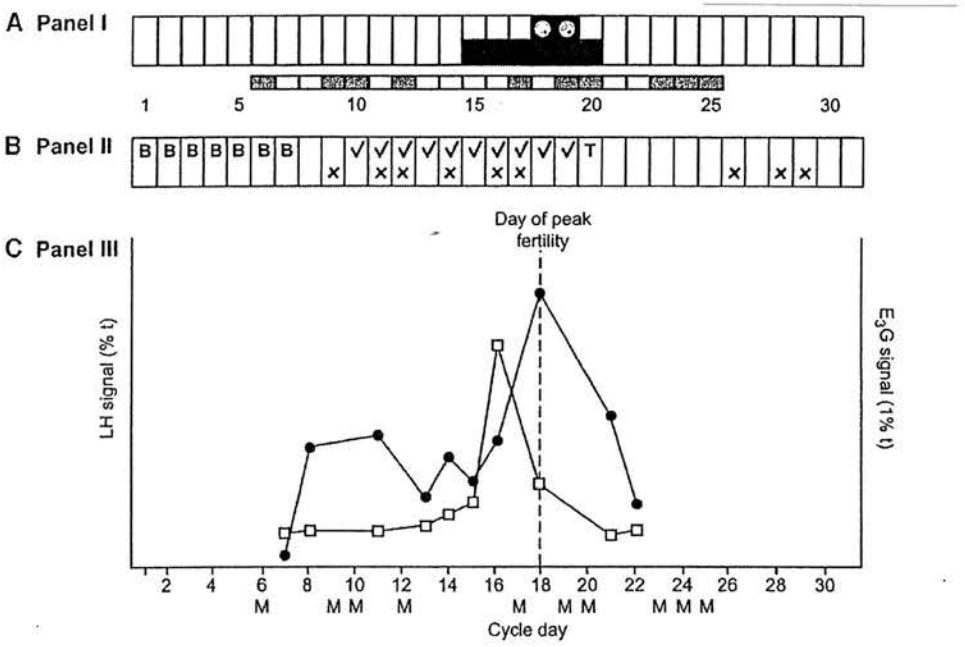
Age was negatively correlated with the percentage of missed tests—younger women missed more tests ($r = -0.36$, $P<.05$). There was no apparent relationship between compliance with the method and the number of pregnancies, number of previous abortions, or number of living children.

### Compliance Among Dropouts

We analyzed cycle data from the seven women who discontinued the study before completion. They missed a significantly higher percentage of tests (44.4%) when compared with the other 25 women who completed the study

FIGURE 1

Information collected from the monitor and the diary card from a woman with a 31-day cycle in which the LH surge was identified. Mifepristone was administered on day 20 (LH+2). (A), Information downloaded from the monitor. Level of fertility displayed to the woman on each day of the cycle: open block, low fertility; partially closed block, high fertility; closed block with circle, peak fertility. Data on testing events appears as a narrower bar underneath: open block, test performed; closed block, test missed. (B), Data recorded on the diary card by the woman (self-report). B, days of vaginal bleeding; check mark, tests done during the critical period; X, days in which sexual intercourse occurred; T, day when mifepristone was taken. (C), Downloaded information on signal levels of LH and estrone-3-glucuronide (E3G) levels. Closed circle, LH; open square, E3G; M, missed tests. Note that on several days (comparing panels A and B), the woman reported performing the test (check mark) when the monitor showed that she did not (M).




*Hapangama. Poor compliance in contraceptive research. Fertil Steril 2001.*

(17.4%; 95% CI of the differences between the two percentages, 10.6–43.3; $t = 3.39$, $P=.002$). The dropouts missed tests on a critical day in 16 of the 22 cycles, although they admitted to missing tests in only four. Therefore, the self-reported incidence of noncompliance during the critical period was 18.1%, whereas the monitor-detected incidence was 72.7%.

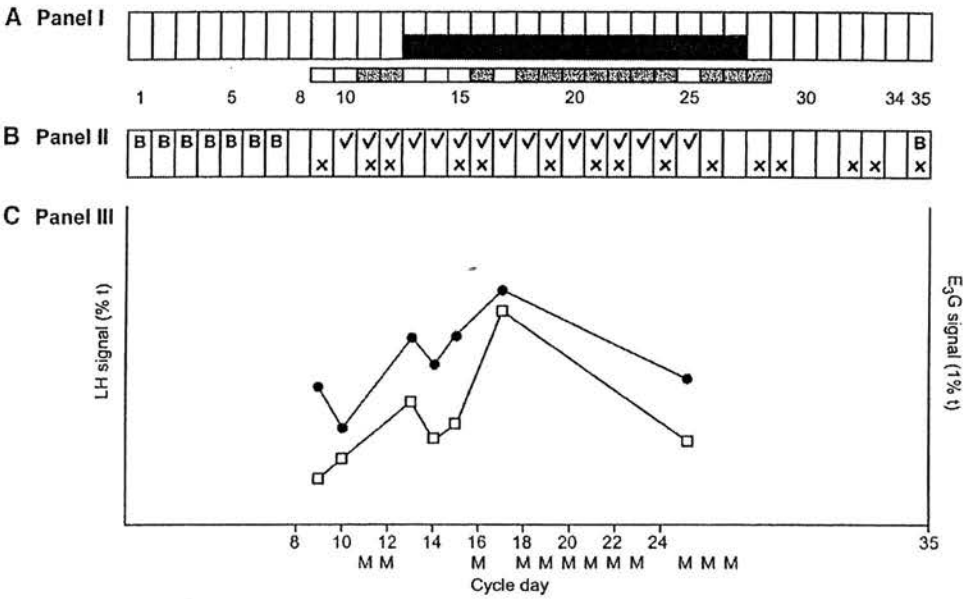
## DISCUSSION

The home use fertility monitor offered us an important methodological advance in providing reliable data on the incidence and the magnitude of noncompliance with the contraceptive method studied and on information about exactly when the imperfect use occurred. We sought to achieve significantly high compliance rates with employing this monitoring system in a contraceptive regimen, which appeared to be acceptable to women (18, 19). Women were counseled at the start of the study regarding the importance of performing urine tests accurately to identify the time to administer mifepristone. They were aware that if mifepristone was not taken, they would be at risk of pregnancy.

Because the teratogenic effects of mifepristone are not known, women considering participation in the study were advised that if pregnancy occurred, they should consider termination. Despite this, the information collected from the monitor demonstrates that women failed to perform 24.2% of the tests in the 162 cycles analyzed. Moreover, in 42% of the cycles, women missed tests during a day that an LH surge was likely to have occurred, in other words, at an absolutely vital time for contraceptive efficacy.

FIGURE 2

Information collected from the monitor and the diary card from a 35-day cycle in the same woman as illustrated in Figure 1. As a consequence of missed tests, the monitor did not identify the LH surge, and mifepristone was not administered. (A), Information downloaded from the monitor. Level of fertility displayed to the woman on each day of the cycle: open block, low fertility; closed block, high fertility. Data on testing events appears as a narrower bar underneath: open block, test performed; closed block, test missed. (B), Data recorded on the diary card by the woman (self-report). B, days of vaginal bleeding; check mark, tests done during the critical period; X, days in which sexual intercourse occurred. (C), Downloaded information on signal levels of LH and estrone-3-glucuronide (E3G) levels. Closed circle, LH; open square, E3G; M, missed tests.




*Hapangama. Poor compliance in contraceptive research. Fertil Steril 2001.*

Although noncompliance is common, by inviting only a selected group of women who appeared to be motivated and committed, we sought to exclude those who might be poor compliers. Interestingly, the medical profession is reportedly poor in identifying noncompliers (20). Users of our method were reasonably young (mean age, 30 years) and were healthy. The serious outcome of noncompliance (pregnancy) was rare. Women may have found the daily requirement for urine testing, using the monitor on a long-term basis, to be complicated or inconvenient. Side effects of the method (although fewer than in most other methods available) may not have been acceptable to them, or they may not have had faith in the effectiveness of the method although this seems unlikely because they did not revert to condoms. Considering these odds, it is not difficult to infer why compliance problems were frequent.

Common sense suggests that with increasing experience, the women may trivialize the need for testing on days during which an LH surge was unlikely to have occurred. All women were made aware of the critical period for testing urine at the start of the study, and as expected, women missed fewer tests during this period. Incomplete understanding of how to be compliant with a regimen has been suggested as a common reason for poor compliance (21). Women in our study were given detailed verbal and written information on using the monitor at the start of the study. The importance of accurate use of the device according to manufacturer's guidelines was stressed at each monthly visit. Because there was no significant difference in the percentage of missed tests between the first study cycle and the last study cycle, it is difficult to support the suggestion that in the earlier cycles, women were less confident about how to use the method or more confident in their ability to guess the correct time for testing (22).

There was a highly significant difference between the patient self-reported percentage of missed tests (2.7%) and that detected by the monitor (15.6%) during the critical period. Figures 1 and 2 illustrate this discrepancy during two cycles contributed

by one woman. This discrepancy was even greater among the seven women who discontinued the study before completion and is consistent with results of previous studies that reported significant overestimation of compliant behavior with self-regulation (23). Patients tend to tell doctors what they think the doctors wish to hear. If they assume that doctors perceive patient nonadherence as a judgmental disappointment, they may feel guilty and fail to report noncompliance.

Although older women tended to miss fewer tests, the other demographic characteristics such as parity, previous abortions, number of living children, and educational background did not correlate with the number of missed tests. Neither did frequency of sexual activity or exposure to the risk of pregnancy correlate with the missed tests. However, because the information about sexual activity was only collected by self-reporting, this association should be accepted with caution.

Most investigators work on the assumption that a patient who complies with one aspect of a clinical protocol (e.g., attending the clinic as directed) also adheres to all other aspects of the study, though this might not always be the case. The monitor supplied data on daily testing of urine, which was only one part of the contraceptive method. We cannot infer from those data how well the women in our study complied with the rest of the protocol, such as recording daily events (sexual intercourse, vaginal bleeding). With no means of testing this, for validity of our results, we had to depend on our volunteers being truthful. Therefore, in the future, we have no other option but to work toward forming a true therapeutic alliance with our volunteers and to come to an agreement with our patients rather than to impose a prescription or a protocol upon them.

In conclusion, the use of microelectronics monitoring systems such as the home use fertility monitor may improve our understanding of the extent of the problem of patient noncompliance, providing precise objective information that no other monitoring technique can produce. This understanding will empower us as health care providers to adopt a no-fault approach to behavior relating to noncompliance and establish "a tailored consensual regimen" with the user that she is able to adhere to (24). This provides the opportunity to make the optimum use of potentially effective treatments and legitimate research evidence. Perhaps a small price to pay for such a return!

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# Therapeutic termination of pregnancy

25

Anna Glasier BSc MD FRCOG

## Introduction

Abortion is common. It has been estimated that 50 million abortions occur worldwide annually – 40% are illegal and around 20 million unsafe. Abortion accounts for between 60 and 120 000 maternal deaths each year (20% of total maternal deaths); almost all are in developing countries and almost all are preventable.

Abortion rates are usually expressed as the number of abortions per 1000 women of reproductive age (15–44 years). Worldwide the average abortion rate is thought to be 32–46/1000 and 10–30/1000 in developed countries. There are wide variations in abortion rates with the lowest being found in the Netherlands (5/1000) and the highest in parts of the former USSR (186/1000). In 1990, in the USA and UK, the rates were 24/1000 and 15.8/1000, respectively.

Abortion rates are related to contraceptive prevalence. Countries with low contraceptive prevalence tend to have higher rates than those where contraceptive use is widespread. In a recent review of the subject, Kulcyzyki and colleagues [1] point out that 'no society has achieved low fertility without recourse to abortion'. Abortion is an intrinsic element of fertility regulation and, as contraceptive prevalence rises in developing countries, so eventually abortion rates fall. However, even in countries where contraceptive prevalence is high and couples have access to methods with low failure rates, abortion is still common. In the UK, where contraception is free of charge and without consultation fees, it has been estimated that 47% of all pregnancies are unintended and 43% of these are terminated [2], amounting to one in five conceptions ending in an abortion. In England and Wales, a woman's average lifetime risk of abortion was calculated by the UK Birth Control Trust to be 43% based on 1995 figures.

After the 1967 Abortion Act in England and Wales, there was a rapid rise in the abortion rate which reached a plateau in the late 1980s. Since then there has been a gradual rise in the rate each year until 1993 when a small downward trend began. In 1994, 166 876 abortions were performed in England and Wales, a 1.1% fall compared with 1993. However, since 1972 the proportion of abortions to conceptions has remained constant at 8% for married women and 37% for single women [3]. In 1996, England and Wales witnessed an 8.3% rise in abortions compared with 1995 (Figure 25.1). The rise was attributed to the 'pill scare' of October 1995, which led to an estimated 5% of women discontinuing their oral contraceptive pills.

## Demographics of abortion

The risk of abortion is related to age, parity, ethnicity and socioeconomic status. Cultural values, laws and policies obviously also play a role. In Western countries the peak age for abortion is 20 and the tendency for young women to be most at risk of abortion is universal. Women over the age of 35 are also more likely to have a pregnancy terminated, perhaps because of the catastrophic domestic and medical consequences of unplanned pregnancy for many women and the decline in the prevalence of effective contraception among this age group.

Marital status also has an effect on abortion risk. In Europe, most women undergoing abortion are

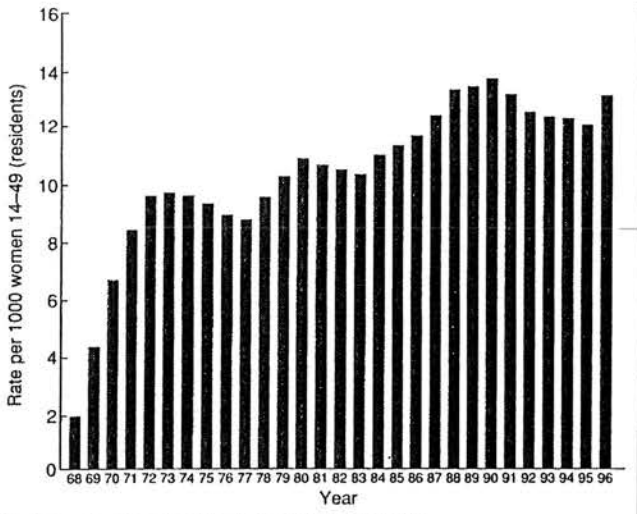



Fig. 25.1 Abortion rates in England and Wales 1968–1996.

unmarried. In England and Wales in the early 1990s, eight pregnancies were terminated for every 100 births among married women compared with 52 per 100 births among unmarried women. In contrast, in Asia, most women are married, while in Africa and Latin America, slightly more married than unmarried women are at risk. The effect of parity is closely related to marital status.

Although data on socioeconomic status are scarce, in general it is true to say that women who are better educated and those who live in urban areas are most likely to undergo abortion. In a recent Scottish survey, Smith and co-workers [4] demonstrated that unplanned pregnancies are commoner among teenagers who live in socially deprived areas than among teenagers from more affluent areas, who, when they do conceive, are more likely to have their pregnancy terminated than their economically deprived peers. In the USA, non-Whites are nearly three times more likely to have a therapeutic abortion, while in the Netherlands, immigrants are significantly more at risk than Dutch women.

With the legalization of abortion and improvements in service delivery, the average gestation at which abortion is performed has fallen. Figures may be misleading, however, since in some countries, abortion may be illegal after 12 weeks, while elsewhere, although legal, it may be much more difficult to obtain after the first trimester.

## Legal issues

From the mid-19th to the mid-20th centuries most developed countries had restrictive or very restrictive abortion laws. Concern about the harmful effects of illegal abortion led to liberalization of the laws. Abortion became legal for 'social reasons' in the USSR in 1920 and in Iceland, Sweden and Denmark in the 1930s, with almost all developed countries, together with China and India, following in the 1960s and 1970s. In the USA, access to abortion, at least during the first trimester, became a constitutional right in 1973. More recently, a swing towards less liberal attitudes and laws has occurred in the USA, and in some central and eastern European countries, particularly Poland and Hungary. Most developing countries have restrictive abortion laws. In Bangladesh, while abortion is illegal, menstrual extraction is available in government clinics up to 8–9 weeks' gestation as long as the pregnancy has not been confirmed.

It has been estimated that 63% of women in the world have access to abortion on request, 12% on broad medical grounds only, while 25% of women must continue the pregnancy unless their life is endangered. Most countries in which abortion is legal require assessment and agreement by at least one doctor, although this may change in the future at least for abortions in the first trimester. In South Africa, recent abortion legislation does not require agreement by a doctor for pregnancies of less than 8 weeks' gestation.

Legalized abortion does not guarantee access to safe abortion. In some countries, such as India, services may be inadequate or too expensive to meet the demand. In the USA, 84% of counties have no specialist medical provider of abortion services. In contrast, in Brazil, where abortion is illegal, it is available in clandestine but safe clinics to women who can afford to pay. In the UK, the law defines

specific indications for abortion which reflect the reasons why a woman finds herself with an unwanted pregnancy. The 1967 Abortion Act and its amendment in the Human Fertilisation and Embryology Act of 1990, states that abortion can be performed if two registered medical practitioners acting in good faith, agree that the pregnancy should be terminated on one or more of the grounds shown in Box 25.1.

The 1990 amendment reduced the upper limit from 28 to 24 weeks' gestation for clauses C and D, reflecting the lowering of the limits of fetal viability resulting from advances in neonatal care. It also included selective reduction in multiple pregnancy cases and authorized the Secretary of State for Health to licence premises for the sole purpose of providing medical termination of pregnancy.

The 1967 Abortion Act does not apply to Northern Ireland, where abortion is only legal under exceptional circumstances, e.g. to save the life of the mother. The law recognizes that some doctors have ethical objections to abortion. Doctors who do have objections should refer women to another colleague who does not hold similar views.

## Adolescents

One-fifth of the world's population is aged between 10 and 19 years, and in some developing countries the majority of the population is under 20 [5]. Everywhere age at first intercourse is falling, while age at marriage is increasing. As a result, teenage pregnancy is becoming common and is widely regarded in many countries as a significant sociomedical problem. In the USA, one million women under 20 become pregnant each year and 82% of these pregnancies are unintended. In Kenya, the percentage of pregnancies among 15–19-year-olds which are mistimed or unwanted is 47% among married women and 74% among those not married.

Young people are less likely to use contraception because they do not expect to have sex, do not know about contraception, lack access to it or lack the ability or power to make decisions. In developing countries, adolescents are more likely to suffer pregnancy-related complications and to die in childbirth than women in their 20s. Abortion-related complications and deaths are also thought to be more common among adolescents than older women. In many countries unwanted pregnancy in an adolescent presents problems with the issue of consent, since the law may require parental consent for the procedure. However, in the UK, if the termination is lawful, consented to by a competent patient and if considered in the teenager's best interests, then a doctor may proceed with the operation if forbidden or unable to obtain parental consent. The issue of competency of minors to give consent is defined in the UK in the Children's Act.

**Box 25.1 Clauses under which abortion is legal in the UK**

A. The continuance of the pregnancy would involve risk to the life of the pregnant woman greater than if the pregnancy were terminated.
B. The termination is necessary to prevent grave permanent injury to the physical or mental health of the pregnant woman.
C. The pregnancy has *not* exceeded its 24th week and the continuance of the pregnancy would involve risk, greater than if the pregnancy were terminated, of injury to the physical or mental health of the pregnant woman.
D. The pregnancy has *not* exceeded its 24th week and that the continuance of the pregnancy would involve risk, greater than if the pregnancy were terminated, of injury to the physical or mental health of the existing child(ren) of the family of the pregnant woman.
E. There is substantial risk that if the child were born it would suffer from such physical or mental abnormalities as to be seriously handicapped.

## Counselling for abortion

The decision to have a pregnancy terminated is never an easy one. All women should have access to abortion counselling, which should provide opportunities for discussion, information, explanation and advice in a manner which is both non-judgemental and non-directive. The way in which counselling is provided will vary; in some developed countries it is mandatory. Whatever the format of counselling, every woman should be given the opportunity to explore her feelings and anxieties, and to make an informed choice. She may be sad about her decision but she should have no long-term regrets. Box 25.2 outlines the management

**Box 25.2 Management and care of the unplanned pregnancy**

1. 'Counselling' – risks and alternatives; inform her that she can change her mind.
2. Assessment of gestation:
   - History
   - Clinical examination
   - Pregnancy test, if indicated
   - Ultrasound, especially if discrepancy between dates and size, suspected adnexal mass or questionable viability
3. Explain:
   - Procedure – medical, surgical, admission and discharge
   - Anaesthetic – GA, LA
   - After effects
   - Complications
   - Contraception
   - Follow-up
4. Document:
   - Reason for termination of pregnancy
   - Gestational age and date of pregnancy test
   - Informed choice with alternatives
   - Discussion of complications and possible sequelae
   - Contraceptive care
   - Tests carried out/offered
5. Tests:
   - Mandatory – haemoglobin, blood group and rhesus status, sickle screen (if indicated) and rubella screen (if indicated, and if follow-up immunization, if required, is feasible)
   - *Chlamydia* and other STD screening, especially in women under 25 years and those who have had a recent change of partner
   - Opportunistic – cervical cytology
   - ?HIV
6. Supply contraception

GA = general anaesthesia; LA = local anaesthesia; STD = sexually transmitted disease; HIV = human immunodeficiency virus.

and care of the unplanned pregnancy at the abortion facility.

Counsellors should encourage the woman to think of both the practical and emotional consequences of all the possible options: abortion, continuing with the pregnancy and adoption. Unless a woman is quite certain of her decision, she will be more likely to regret it later. A few women will need more time and perhaps more counselling to help them make up their minds. Some women will change their minds. The incidence of long-term regret/emotional sequelae is low.

Even in countries where abortion is legal and accessible, many women fear they may be refused an abortion and, perhaps, for some, it is not possible to make the final decision until they are quite certain that they really do have a choice. For others, the reality of abortion may not become apparent until they are faced with the practicalities of undergoing the procedure. In some countries, such as France, statute demands a waiting period between the time the abortion has been agreed and the time it is carried out, to allow women the opportunity to reflect on their decision free from the worry that the request may be refused.

The majority of women (around 80%) have made their decision before they see a doctor. Seeing the doctor is usually a necessary part of obtaining an abortion and women attend expecting confirmation of their pregnancy, information and referral to an abortion provider. The skill of the counsellor lies in the ability to detect those women who need lengthy discussions and more support, and those who may be at risk of severe regret.

The different techniques, together with their advantages and disadvantages, should be discussed to enable a choice to be made where available and appropriate. The risks of abortion together with the effect of abortion on future fertility should be covered. Women also need to receive information about what happens after the abortion, the expected duration of bleeding, when to have intercourse and even such details as when to have a bath. The decision to have a termination has often arisen because a relationship has ended and the woman may not see an immediate need for future contraception. While discussion about future contraception prior to or even immediately after the abortion may not be ideal, in some cases it may be the only chance the professional has. Contraception is an important issue in post-abortion care and follow-up.

## Medical assessment

### *Medical history*

Particular attention should be paid to conditions such as asthma, which may influence the choice of method of abortion, and to factors which may increase the risks of the procedure such as previous thromboembolic disease.

### *Gestation*

Gestation should be determined by menstrual history and pelvic examination. A pelvic ultrasound

scan is unnecessary unless there is doubt about the gestation or ectopic pregnancy is suspected.

### *Genital tract infection (particularly* Chlamydia)

Whether screening is performed or everyone is treated with prophylactic antibiotics depends on the background incidence of infection in the local population and on the relative costs. If screen is positive, antibiotic therapy should be started *before* the abortion is performed. In high-risk populations, both screening (and wherever possible, contact tracing) and antibiotic prophylaxis may be justified. Antibiotic prophylaxis should comprise anti-chlamydial and antianaerobic infection agents. There is evidence that antibiotic prophylaxis for high-risk cases reduces the incidence of infection [6].

### *Hepatitis B and HIV*

Women considered to be at high risk of hepatitis B or HIV should be offered screening with appropriate counselling. Women who refuse screening should be treated as high risk during the abortion procedure.

### *Cervical screening*

Cervical screening is not essential and may not be practical, but should be offered in accordance with national screening policies.

### *Haemoglobin and blood group*

Haemoglobin concentration and blood group should be determined. Women who are rhesus negative should be injected with anti-D immunoglobulin (1250 IU) before or within 48 h of the abortion to prevent the development of rhesus isoimmunization.

**Box 25.3 Methods for inducing abortion**

Early first trimester (≤ 9 weeks)

Surgical
- Menstrual regulation
- Vacuum aspiration

Medical
- Antiprogesterones + prostaglandins
- Methotrexate + prostaglandins
- Prostaglandins alone (not currently recommended)

Late first trimester (9–14 weeks)

Surgical
- Vacuum aspiration

Second trimester (beyond 14 weeks)

Surgical
- Dilatation and evacuation
- Hysterotomy

Medical
- Intrauterine irritants
- Prostaglandins

## Methods of terminating pregnancy

There is a variety of methods available for termination of pregnancy (Box 25.3). The method chosen depends largely on gestation and availability of methods (Figure 25.2). The woman's parity, medical history and her wishes are other issues to consider.

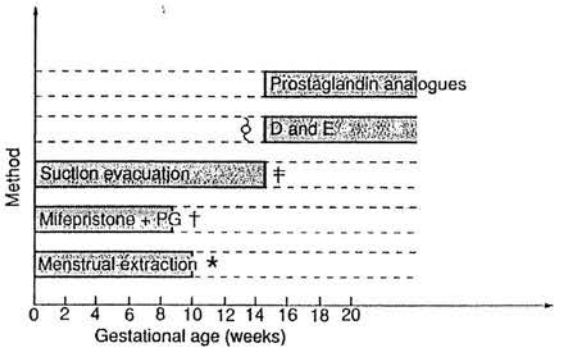
## Early first trimester (up to 9 weeks)

### *Surgical methods*

#### *Menstrual regulation*

In some countries women who have missed a menstrual period

Fig. 25.2 Methods of termination of pregnancy by gestational age. PG = prostaglandin.




*No anaesthesia required to 6 weeks, local anaesthetic thereafter.
†Mifepristone is also licensed in UK for medical termination of pregnancies 12–20 weeks' gestation.
‡Can be done under local or general anaesthetic. Cervical priming using prostaglandins, mifepristone or hydrophilic dilators is recommended for nulliparous women over 10 weeks' gestation.
§Cervical priming essential.

have access to menstrual regulation, when suction evacuation of the uterine cavity is performed usually without confirmation of pregnancy. This method is common in China, where abortion is legal, and in Bangladesh up to 6–9 weeks of amenorrhoea. Usually undertaken very soon after the missed menstrual period, it is done with a hand-held syringe attached to a manual or electrical aspiration pump.

### *Vacuum aspiration*

Vacuum aspiration has been the method of choice for early surgical termination of pregnancy in most developed countries for over 20 years. Dilatation and curettage is not recommended as it requires a greater degree of cervical dilatation, and is associated with a significantly higher incidence of uterine injury and of retained products of conception. Vacuum aspiration can be performed under either local paracervical block (LA) or general anaesthesia (GA). Some evidence suggests that local anaesthesia may be safer: in the USA, the mortality rate is 2–4 times greater when general rather than local anaesthesia is used for first-trimester abortion. In the UK, where most abortions are performed under general anaesthesia, there has not been an abortion-related maternal death in many years. In developing countries, economic considerations and the availability of skilled personnel may influence the choice of anaesthetic.

Preoperative treatment with a cervical priming agent reduces the risk of haemorrhage and genital tract trauma. Prostaglandins, bougies and the antiprogesterone RU486 (mifepristone) are all effective, but prostaglandins probably have a faster onset of action. Pretreatment of the cervix increases the cost of the procedure and may be difficult to organize when abortion is performed as a day case. As cervical trauma is commoner in women under the age of 17 years and uterine perforation is associated with increasing parity and increasing gestation, efforts to arrange cervical ripening should be concentrated on very young women, highly parous women and those presenting at later gestation.

A curette of 6–10 mm internal diameter is passed through the cervix and the contents of the uterus aspirated using negative pressure. It is advisable to use the smallest diameter curette which is adequate for the gestation – 8 mm at 8 weeks, 10 mm at 10 weeks. The curette may be made of metal or plastic, curved or straight, and either flexible or rigid.

Vacuum aspiration at this stage of pregnancy is safe, with an incomplete abortion rate of less than 2%. Failure is more likely to occur before 7 weeks' gestation when the fetus may be missed by the curette. Thus it may be better to defer operation until after 7 weeks or to use medical methods. The mortality from vacuum aspiration in the first trimester is less than about 1 per 100 000, considerably less than the maternal mortality from continuing pregnancy.

### *Medical methods*

A variety of compounds have been used to induce abortion medically rather than surgically (Figure 25.2).

### *Prostaglandins*

Prostaglandins stimulate uterine contractions, and can be administered orally, vaginally, extra-amniotically, intra-amniotically or by intramuscular injection. In the early first trimester, prostaglandins alone will induce complete abortion in up to 95% of cases, but the duration of treatment and the incidence of side effects militate against their routine use.

### *Antiprogesterones*

Antiprogesterones are synthetic steroids which block the action of progesterone by binding to its receptor. Mifepristone (RU486, Mifegyne) is the only such compound yet marketed and is used in France, China, UK and Sweden. In 1996 it was recommended to the US Food and Drugs Administration as a safe and effective means of inducing abortion, although it is as yet not available for use in the USA. Mifepristone also binds to the glucocorticoid receptor and blocks the action of cortisol.

When mifepristone is used alone, for pregnancies with up to 63 days of amenorrhoea, complete abortion only occurs in around 60% of cases. The antiprogesterone itself stimulates some uterine contractility but also greatly enhances the sensitivity of the myometrium to prostaglandins. The rate of complete abortion rises to over 95% if a prostaglandin analogue is given 36 or 48 h after the administration of mifepristone. In the UK, the recommended regimen is mifepristone given as a single oral dose of 600 mg (3 × 200 mg tablets) followed 48 h

later by a 1 mg vaginal pessary of the prostaglandin Cervagem (gemeprost) (Figure 25.3). Mifepristone 200 mg has been shown to be equally effective and since this makes the regimen considerably cheaper, the lower dose is now widely used. In the UK, mifepristone is also licensed for use with gemeprost for termination of second-trimester pregnancies and for management of death *in utero* in the third trimester. Its use in the pretreatment of the cervix prior to surgical termination has already been discussed.

Misoprostol, an oral prostaglandin $E_1$ analogue, marketed for the treatment of peptic ulcer, has been shown to be effective in combination with mifepristone, although efficacy may decline after 7 weeks' gestation. Unlike gemeprost, it does not require refrigeration and 'thawing' for an hour prior to administration. Misoprostol can be administered vaginally or orally, and may be more effective vaginally, but randomized controlled studies are few. In the UK, misoprostol is not licensed for termination of pregnancy. The cost of misoprostol is 50 times less than gemeprost. Misoprostol has also been used with mifepristone in the termination of second-trimester pregnancies.

**Box 25.4 Contraindications to first-trimester medical abortion using antiprogesterone + prostaglandins**

Absolute contraindications
- > 9 weeks' gestation
- Suspected ectopic pregnancy
- Active asthma
- Liver and/or renal disease
- Suspected adrenal insufficiency
- Heavy smoking (>15 cigarettes per day) *and* > 35 years
- Unavailability for follow-up within 2 weeks
- Anaemia (Hb < 10 g/dl)
- Haemolytic disease or taking anticoagulants

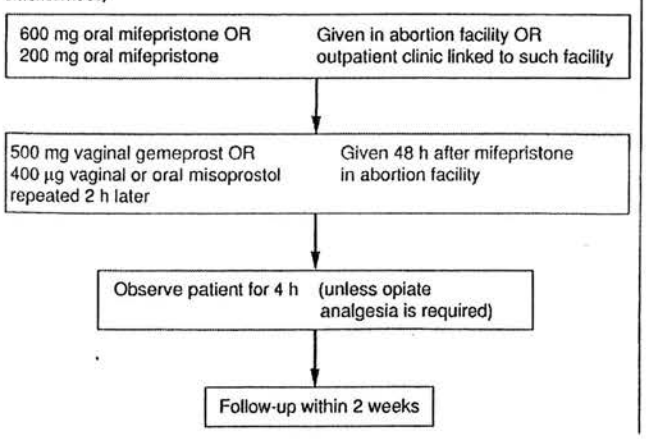
Relative contraindications
- > 8 weeks' gestation
- Hypertension (diastolic pressure > 100 mmHg)
- Heavy smoking (> 15 cigarettes per day)
- > 35 years
- Women taking systemic steroids

Not all women are suitable for medical abortion. The contraindications are shown in Box 25.4.

There are very few side effects following the administration of mifepristone. The fetus is usually aborted following the administration of prostaglandins, and this is accompanied by bleeding and pain. The bleeding is usually like a heavy period, although rarely (<1%) there may be very heavy bleeding requiring resuscitation. The amount of bleeding is related to gestation, since the size of the placental site increases as pregnancy advances. Nulliparous women and those with a history of dysmenorrhoea are more likely to experience severe pain and 10–20% of women may need opiate analgesia; the rest will cope with paracetamol alone. Prostaglandin synthetase inhibitors, such as aspirin or mefenamic acid, should be avoided. Bleeding can continue for up to 20 days after the abortion, although in most women bleeding stops after 10 days. The total amount of blood lost is similar to that occurring at the time of vacuum aspiration.

A follow-up visit about 2 weeks after administration of the prostaglandin is essential because 30% of women do not pass an identifiable fetus and/or placental tissue. Ongoing pregnancy occurs in only 1% of cases; however, evacuation of the uterus will be

**Fig. 25.3 Protocol for medical termination of early pregnancy (≤ 63 days' amenorrhoea)**



necessary in up to 5% because of incomplete abortion. These figures are no different from those associated with surgical abortion.

The risk of fetal malformation following RU486 alone or in combination with prostaglandins is unknown. Women should be advised that medical abortion is a two-stage procedure, and that it is not possible to have a change of heart after taking RU486 and before prostaglandin administration. In the event of a failed medical abortion, the woman must be strongly advised to have vacuum aspiration, although babies born to the few women who have chosen to continue with the pregnancy, after medical abortion has failed, have been normal. Misoprostol is teratogenic; however, any congenital defect may partly be the consequence of the failed abortion.

In France and the UK, around 20–25% prefer medical abortion. Women often choose the medical method because it usually avoids an anaesthetic and because they feel more in control of the situation. Some women, however, find the two stages a disadvantage. The incidence of serious complications is probably similar to that associated with surgical abortion but, because 95% of women need neither anaesthesia nor instrumentation of the uterus, large randomized trials may eventually show medical abortion to be safer.

#### *Methotrexate*

The cytotoxic drug methotrexate has recently been used in the medical management of ectopic pregnancy. In the USA, methotrexate has been proposed as an effective adjuvant to prostaglandins used for first-trimester abortion. Unlike RU486, methotrexate is known to be teratogenic, thus risking fetal malformation and inevitable litigation in the event of ongoing pregnancy.



## Late first trimester (9–14 weeks)

At this stage of pregnancy, the method of choice is vacuum aspiration, which can be done under local or general anaesthesia. Although abortion can be induced by antigestagens and prostaglandins, the incidence of incomplete abortion is high. The cervix should be pretreated at gestations of greater than 10 weeks in nulliparous women. Although vacuum aspiration is an extremely safe operation, the incidence of complications rises as gestation advances.

## Beyond 14 weeks

### *Surgical methods*

#### *Dilatation and evacuation (D&E)*

In some countries, including the USA, D&E is commonly used for terminating pregnancies up to 20 weeks' gestation. It should only be performed by experienced surgeons. Under local or general anaesthetic, the cervix is dilated to 14 mm or more to allow removal of relatively large fetal parts. Pretreatment cervical priming is essential and an oxytocin infusion during D&E is advisable to reduce blood loss. Fetal parts should be kept so that the completeness of the procedure can be checked before evacuating the cavity with a 12 mm suction curette. D&E is thought to be safer than intra-amniotic instillations up to 16 weeks' gestation, although the procedure has not been compared with vaginal prostaglandins.

#### *Hysterotomy*

The removal of the uterine contents via laparotomy and a vertical or transverse uterine incision is associated with relatively high mortality and is rarely necessary, particularly as the presence of a uterine scar may compromise future pregnancies.

### *Medical methods*

#### *Intrauterine irritants*

Hypertonic saline and urea can be administered intra-amniotically to induce late abortion. The procedure is prolonged but can be shortened by pretreatment cervical priming and the use of intravenous oxytocin to enhance uterine contractions. The incidence of infection, haemorrhage and retained products of conception is higher than with prostaglandins but the fetus is rarely delivered alive. Rarely, disseminated coagulopathy may occur and the inadvertent systemic administration of hypertonic saline may lead to cardiovascular collapse. Another agent, ethacridine lactate (Rivanol) is an acridine dye which can be inserted into the extra-amniotic space. It is cheap, safe and weakly antiseptic and, for these reasons, is popular in some developing countries. There is some evidence of acute toxicity in animals and, for this reason, WHO has denied permission for clinical trials.

### *Prostaglandins*

Prostaglandins alone have been widely used in the termination of second-trimester pregnancy. Intra-amniotic administration requires skilled personnel. Rarely, acute systemic absorption may cause hypotensive crisis, myocardial infarction, cerebral haemorrhage, bronchospasm and death. The induction–abortion interval is prolonged with a concomitant increase in the risk of infection. The experience is painful. The vaginal administration of pessaries containing a prostaglandin $E_1$ analogue or misoprostol is safer and less unpleasant. In the UK, this approach is now routinely preceded by pretreatment with the antiprogesterone RU486 (mifepristone), which significantly shortens the interval between administration of the prostaglandin and abortion of the fetus to 6–8 hours. Mifepristone 600 mg is given 36 h before vaginal insertion of a 1 mg gemeprost pessary repeated at intervals of 3 and 6 h until expulsion of the fetus occurs. Infusion of prostaglandin $E_2$ into the extra-amniotic space can be used if pessaries are not available. Overall, 30% of women retain all or part of the placenta, and require surgical evacuation of the uterus.

Despite some disadvantages, medical abortion with prostaglandins alone, or preferably in combination with mifepristone, is very effective and associated with a very low incidence of complications. Because it requires less surgical skill, the potential for serious complications is probably less than for D&E and hence, it will continue to be used in many parts of the world.

Abortion beyond 18 weeks' gestation is rare and is usually reserved for pregnancies complicated by severe fetal malformation. Particularly distressing for both the mother and the staff, these late abortions are often effectively managed with vaginal prostaglandins in combination with RU486, with intra-amniotic urea or fetal intracardiac injection of potassium to minimize the chances of expulsion of a live fetus (see Chapter 33 for information about anaesthesia for termination of pregnancy). Box 25.5 gives details of cervical preparation.

## Sequelae of abortion

In developed countries where abortion is legal, associated mortality and morbidity have fallen over the last two decades. In Europe and the USA, the risk of death is less than 2 per 100 000 procedures; in Sweden, abortion is ten times safer than childbirth. The risks rise with gestation. Serious complication rates for first-trimester abortions are less than 1% (Box 25.6), with fewer than 1 in 1000 women needing hospitalization; beyond 10 weeks' gestation the health risks of abortion rise with each week. The risk of late second-trimester abortion is up to four times higher than that for first-trimester abortion. Complications are usually divided into immediate (during or within 3 h of the procedure), delayed (3 h to 28 days) and late (>28 days) (Box 25.7).

**Box 25.5 Preparation of the cervix**

I. Hydrophilic dilators
Reduce the force needed for dilatation

(a) Laminaria tents:
- Stems of seaweed
- Radial force on the cervix
- Swell to 3–4 × their size
- Cheap
- Never 100% sterile
- Slow action (6–48 h)

(b) Synthetic dilators:
- Rapid dilatation

(i) Lamicel
- Polyvinyl sponge containing 450 mg of $MgSO_4$; 3 and 5 mm sizes
- Force not radial, therefore not useful for late abortions
- Maximum action after 2 h

(ii) Dilapan
- Hypan dilator – radial force
- Quick action
- 4–8 mm in 30 min
- 12 mm in 1 h

II. Prostaglandins
e.g. Gemeprost 1 mg pessary 1–3 h preoperatively produces dilatation of 7–9 mm; or misoprostol orally

III. Foley catheter
Inserted intracervically and balloon inflated with 20–30 ml of water; left overnight

IV. Mifepristone

**Box 25.6 Complication rates (first-trimester abortion)**

| | |
|---|---|
| Infection | 2–5% |
| Cervical laceration | <1–3.5% |
| Incomplete abortion | <1–19% |
| Uterine perforation | <1–1.3% |
| Haemorrhage | <1–2.5% |

## Immediate complications

### *Trauma*

Cervical laceration occurs usually when the tenaculum pulls off the cervix during dilatation. The risk is reduced by preoperative cervical priming and by placing the tenaculum vertically with one tooth in the os and the other high on the anterior lip, taking a 'big bite' of tissue. If laceration occurs, it may require suturing but, more commonly, simple postoperative observation is all that is needed.

Uterine perforation probably occurs more commonly than is apparent: perhaps as many as one in six perforations goes undiagnosed. When recognized, perforation is usually without complications and the patient should simply be observed. If intra-abdominal trauma is suspected – more likely during second- than first-trimester termination – laparoscopy and/or laparotomy should be performed and the damage repaired by a competent surgeon.

**Box 25.7 Sequelae of induced abortion**

Immediate
- Trauma
- Haemorrhage
- Amniotic fluid embolism
- Anaesthetic complications

Delayed
- Incomplete abortion
- Unrecognized ectopic pregnancy
- Infection
- Venous thromboembolism

Late
- Reproductive sequelae
- Psychological sequelae

### *Haemorrhage*

The true incidence of haemorrhage depends on the definition used. Management includes blood transfusion, paracervical injection of vasopressin solution, hysteroscopy and internal compression of the uterine cavity with the balloon of a Foley catheter or with a pack soaked in vasopressin solution. Coagulopathy rarely complicates abortion.

### *Amniotic fluid embolism*

This is a rare but potentially fatal complication of second-trimester abortion. The risk may be reduced by draining the amniotic fluid at the beginning of the procedure.

### *Anaesthetic complications*

In the USA, complications of general anaesthesia are the leading cause of abortion-related death. In a recent review of the subject, Grimes [7] concluded that abortion under local anaesthesia is preferable in terms of both safety and cost. Abortion in the UK is still predominantly managed with general anaesthesia. Offered the choice, some women would certainly find the idea of being awake during the procedure quite unacceptable. However, up to 30% of women in the first trimester choose local anaesthesia when offered.

### *Venous thromboembolism*

Pregnancy increases the risk of thromboembolism; so does general anaesthesia. Most women undergoing termination of pregnancy are young and physically fit, and surgical abortion is rarely a prolonged procedure. Nonetheless, the risk of venous thrombosis should never be overlooked and a previous history of thromboembolism might determine the choice of anaesthetic and, if practical and available, the method of inducing abortion.

## Delayed complications

### *Incomplete abortion*

The commonest complication following abortion is the persistence of placental and/or fetal tissue. Up to 5% of women undergoing first-trimester medical abortion will require surgical re-evacuation of the uterus within the first month.

The incidence of incomplete abortion after vacuum aspiration rises with gestation. Bleeding 2 weeks after a medical or surgical abortion is not in itself an indication to evacuate the uterus. Ultrasound scans often show residual trophoblastic tissue even in women who have stopped bleeding. Although an ultrasound scan of the uterus and the measurement of human chorionic gonadotrophin (HCG) in plasma may be helpful in diagnosing an ongoing pregnancy, the decision to evacuate the uterus should be made on clinical grounds, i.e. continued heavy or persistent bleeding from a bulky uterus in which the cervix is still dilated. The majority of women with an incomplete or missed abortion will pass the residual tissue with

time if they will wait. The belief that all women with an incomplete abortion have a high risk of intrauterine infection until the uterus is evacuated probably stemmed from the time when illegal abortion was common.

### *Unrecognized ectopic pregnancy*

Examination of aspirated tissue for chorionic villi and fetal parts should reduce the risk of unrecognized ectopic pregnancy which may be fatal. Microscopic (pathological) examination of the specimen is only indicated if a molar pregnancy is suspected.

### *Infection*

Post-abortion infection is probably also under-reported but should be suspected in a woman with prolonged heavy vaginal bleeding as well as those with classical symptoms of pain and pyrexia. Established pelvic inflammatory disease with pyrexia, abdominal pain and offensive vaginal discharge occurs in around 1% of women whatever method of abortion is used. The risk can be reduced by pre-abortion screening and/or prophylactic antibiotics as discussed earlier.

## Late complications

### *Reproductive sequelae*

Almost all studies [8,9], agree that neither vacuum aspiration nor second-trimester prostaglandin abortion is associated with a significant increase in secondary subfertility. There is a 30% risk of tubal infertility following severe post-abortion infection. The latter is uncommon occurring in <0.5% of cases. There are as yet insufficient data on first-trimester medical abortion, but there is no reason to suspect that the risk will be different. Uncomplicated induced abortion does not increase the risk of ectopic pregnancy, nor of spontaneous abortion unless sharp curettage is used. Abortion has no effect on the outcome of subsequent pregnancies continued to childbirth, such as low birth weight or premature delivery. The data on the increased risk of placenta praevia following induced abortion are inconclusive. Ashermann's syndrome is a rare complication of abortion where intrauterine adhesions follow vigorous curettage of the uterine wall. Management is hysteroscopic division of the adhesions, placement of a Foley catheter or an intrauterine device *in utero* and treatment with a short course of oestrogen/progestogen.

### *Psychological sequelae*

Many women feel emotional for a few days following the abortion. Many studies have, however, demonstrated a significant improvement in psychological well-being by 3 months after, compared with before the abortion [10]. There is no evidence of an increase in the incidence of serious psychiatric problems following abortion: indeed a recent review of the subject [11] concluded that 'there is, as yet, no credible evidence for the existence of post-abortion syndrome'. In contrast, the incidence of depression, suicide and child abuse is higher in women who have continued with the pregnancy because abortion was refused [12]. In the same study, the children born to women refused abortions had higher incidences of psychopathology and educational and social problems than their matched contemporaries, and these differences persisted into adulthood.

### *Breast cancer*

Induced abortion does not seem to increase the risk of breast cancer [13].

## Follow-up

All women should have their questions answered and receive contraceptive advice (Table 25.1) and, if appropriate, supplies before leaving the abortion facility. All

**Table 25.1** Post-TOP contraception

| Method | When to start? |
|---|---|
| Combined pill | Day of operation or following day |
| Progestogen-only pill | Day of operation or following day |
| Condom | Advisable whenever intercourse occurs for STI prevention |
| IUD | At operation (if ≤ 12 weeks) or at next menses |
| Diaphragm | Check size ≥ 2 weeks post-TOP |
| Depo-Provera | Within 5 days of TOP |
| Norplant | At operation |
| Sterilization | Discussed as for interval procedures |

STI = sexually transmitted infection; IUD = intrauterine device; TOP = termination of pregnancy

should be given a follow-up appointment within 3 weeks, either with the clinic which carried out the abortion or with a suitable alternative doctor. At follow-up, a pelvic examination should aim to confirm complete abortion and the absence of infection. Discussion should include contraceptive advice and post-abortion counselling if required.

## The future

In the foreseeable future, the important changes in the management of unwanted pregnancy are likely to be political rather than clinical. Clinical scientists will continue to tinker with regimens for medical abortion in an attempt, for example, to find the 'perfect' prostaglandin, which is free from side effects or to develop slow-release prostaglandins to be given at the same time as mifepristone. A number of pharmaceutical companies have antiprogesterone drugs which may be superior to mifepristone. Most, however, seem reluctant to develop them as abortifacients because of the politics of abortion.

Women's health advocates and some non-governmental organizations are pressing for widespread availability of medical abortion, particularly in developing countries where surgical techniques may be dangerous, and where abortion-related morbidity and mortality are high. In this context, there is also a move to facilitate the use of medical methods by individual women in their own homes. Many doctors have concerns about the safety of do-it-yourself medical abortion but, seen as a wider public health imperative, persuasive arguments can be made at least for reducing the need for medical supervision for some stages of medical abortion procedures. There is, however, a risk that moves to allow abortion at home will increase popular support of the anti-abortion lobby and, in developed countries, where safe abortion is available and accessible, it may be sensible not to 'rock the boat'.

Finally, it is likely that abortion legislation will continue to change throughout the world. In developing countries, where abortion is currently illegal, the inevitable processes of liberalisation – as in South Africa – may result in legalisation. In Europe, where birth rates have fallen in some countries to below replacement level, it is equally possible that governmental concerns about demographic changes may result in abortion becoming less easily available. Whatever happens, we can rest assured that in no country will abortion ever be out of the headlines.

## Resource list

### Further reading for healthcare professionals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Current OBSTETRICS & GYNAECOLOGY

Mini-symposium: Therapeutic abortion

# The organisation of abortion services

A. Glasier

**The availability and genuine accessibility of abortion varies widely throughout the United Kingdom depending mainly on the commitment and interests of local gynaecologists. In most districts in England and Wales availability falls far short of that recommended by successive governments. Arguments can be made in support of the provision of abortion either as part of general gynaecology services or within dedicated units. Within each district one consultant should have a special responsibility for all aspects of fertility control including abortion. The establishment of a service for medical termination of pregnancy in each district is desirable and may reduce the burden on surgical gynaecology. Medical abortion is only available to women referred in early pregnancy, so that efficient referral is in the interests of the patient and the service. This may be best achieved by some form of centralisation of appointments.**

## Introduction

Induced abortion has been legal throughout the United Kingdom for 25 years. The number of women undergoing pregnancy termination rose in England and Wales from 24000 in 1967 to 184000 in 1989. In this review the overall provision of services will be described and the organisation of each stage of the procedure discussed.

## Provision of services

The provision of abortion services varies enormously across the country. In Scotland over 97% of the 10192 abortions performed in 1989 were done in NHS premises, compared with only 41.5% in England and Wales, where just over 50% of abortions were done privately and 9% by agencies who are paid by the NHS. In the West Midlands Health Authority less than 14% of abortions were done on NHS premises.

In 1974 the Lane Committee,[1] set up by the government to review the working of the 1967 Abortion Act, recommended that contractural arrangements with other agencies should only be used, if at all, to provide temporary facilities. In 1979 the Merrison report[2] recommended that 75% of abortions should be provided free in NHS facilities. In England and Wales that target has never been reached. With the current changes in the NHS, even this level of service is under threat. An article in the Health Service Journal published in 1990[3] reported that abortion services were facing widespread reductions and cited West Lambeth Health Authority where the number of abortions paid for by the NHS had been reduced from 26/week to 9/week. In a country where abortion is legal, the adequate provision of services depends on governments, health authorities and gynaecologists recognising that abortion is a fundamental component of a woman's ability to control her own fertility. A genuinely accessible service can be provided – as appears to be the case in Scotland – if the commitment is there.

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Maresh[4] found no relationship between the number of beds or of gynaecological sessions and the regional variation. In a more recent study undertaken in 1989[5] few gynaecologists appeared to think that there was a problem of clinical resources. In reality the uneven spread of abortion services across the country reflects the varying degree of commitment and it is largely the local gynaecologists who decide how accessible abortion is. Throughout the 1960s and 1970s the professor of obstetrics in Grampian was a strong supporter of abortion[6] and the service provided was – and still is – comprehensive. In contrast the professor in Glasgow during the same years was totally against abortion and it is only recently that the majority of abortions have been done within the NHS in the West of Scotland.

Some gynaecologists dislike doing abortions[5,7] which they regard as occupying outpatient and theatre time otherwise available for 'real gynaecology'. In the Francombe survey 60% of gynaecologists questioned wanted to see abortion split from general gynaecology and 45% favoured regional abortion units. The majority of gynaecologists in Scotland, however, did not wish to see abortion being carried out separately from general gynaecology. Gynaecologists in Scotland provide an efficient abortion service within a general gynaecological setting – perhaps when the system works well the benefits are more obvious.

In some parts of the country dedicated abortion units do exist and they work well, however the Lane Committee did not favour the establishment of separate units but rather recommended a general improvement of all gynaecological services. In her report on Patterns of Hospital Medical Staffing, Dowie[8] argues that the workload of gynaecologists has changed dramatically since 1974. New services such as colposcopy have been introduced and departments providing the full range of services including abortions are overstretched. One solution, suggests Dowie, would be to transfer work associated with pregnancy termination to dedicated units. There are advantages to dedicated units. On general gynaecological operating lists suction terminations tend to be left until the end when they are often done by juniors who may be unsupervised, the consultant having left to fulfil another commitment. Abortions done within the NHS are associated with a higher morbidity than those done in the private sector.[9] Abortions done privately are more likely to be done at an earlier gestation but it may also reflect the relative inexperience of those most likely to perform the surgery under the NHS. Those in favour of specialised abortion units argue that the volume of work – usually undertaken by one or two interested surgeons – means that it is being done by experts. This may be particularly important when less commonly used procedures such as dilatation and evacuation for second trimester abortion are called for. The establishment of abortion clinics also avoids the necessity for women undergoing abortions occupying beds next to women undergoing other procedures – infertility investigations for example. It is also argued that the staff working in these units are inclined to be much more sympathetic and that they are better placed and more likely to undertake contraceptive counselling.

However, this approach separates abortion from all other areas of reproductive health care turning it into something special and different. Counselling for and performing abortions should be part of the training of all gynaecologists and in a general gynaecological setting medical students and doctors planning to enter general practice are exposed to all aspects of the care of women with unplanned pregnancy. Few people want to spend all their time doing abortions and, moreover, general gynaecological services are better equipped to cope with complications of abortion. The district general hospital is often more accessible to women and more acceptable to those who wish to conceal the fact that they are having an abortion. Perhaps more importantly, if abortion is provided locally and is recognised as a local issue, it is more likely to highlight local needs in all areas of fertility control. Finally, a separate abortion unit becomes an easy target for the anti-abortionists as has happened in the USA. In their Working Party Report on Unplanned Pregnancy[10] the Royal College of Obstetricians and Gynaecologists (RCOG) recommends that a senior specialist in each Health Authority should oversee the provision of contraception, sterilisation and legal abortions. The report suggests that community gynaecologists may fulfil this role. At present there are very few community gynaecologists and they come from a variety of backgrounds. If abortion is to be provided as part of the general gynaecological service the specialist responsible for its organisation must have status equivalent to those who are providing the service but the status of community gynaecologists is as yet undefined.

If there was more widespread recognition of the size of workload undertaken by gynaecologists, the great majority of whom have a substantial obstetric case-load, a significant increase in consultant numbers together with the appointment of one consultant in each Health Authority with responsibility for fertility control would ensure the organisation of efficient abortion services. In the conclusions to her Report on Medical Staffing Dowie suggests the establishment of centres to undertake gynaecological procedures that can be performed on an outpatient or day care basis including abortion, colposcopy, sterilisation and the investigation of infertility.[8]

Centres for Women's Health could include all these services together with well woman and family planning clinics, breast screening and facilities for health education and health promotion. Such centres would provide opportunities for training and for integrated

research into all aspects of women's health including abortion.

### Organisation of the service

In 1991 the Birth Control Trust (BCT) published a specification for a model abortion service.[11] The document reminded Health Authorities that the overall aim is 'to provide an efficient, effective and comprehensive service which is of demonstrably high quality'.

A comprehensive service begins with the initial presentation of the woman with an unplanned pregnancy.

### Initial presentation

The majority of women requesting pregnancy termination initially seek help from their general practitioner. Others present to community family planning clinics or to organisations such as Brook Advisory Centres or the British Pregnancy Advisory Service. The government has always recognised the need for women to be able to discuss and obtain contraception and fertility regulation from someone other than their general practitioner. Unfortunately, the widespread reduction in NHS community family planning clinics in some parts of the country[12] jeopardises this aspect of an accessible abortion service. Not only are such clinics known to provide special services for women under 20 – a group in whom the abortion rate is high – but they are also seen as an essential resource in reducing the number of unwanted pregnancies particularly by providing emergency contraception.

Pregnancy diagnosis, advice and counselling are undertaken at the first visit. Not all general practitioners have the capacity to undertake pregnancy testing in their surgeries. David Paintin[13] reported that only 30% of GPs were able to do immediate pregnancy testing. Waiting for test results can lead to delays of up to 1 week before a woman is referred. In the absence of pregnancy testing facilities, a history of amenorrhoea and symptoms of pregnancy are sufficient to warrant referral if the pregnancy is unwanted.

Most women seeking abortion are fairly certain of their decision at the time of initial presentation. Nevertheless, every woman should have the opportunity to discuss her feelings about the pregnancy, the alternatives and to obtain information about procedures involved in abortion.

It has been estimated that about 10% of women will need further counselling at the time of referral and a small number may require help from a trained counsellor with more time and skills available than the average GP. In a review of 735 referrals to an Edinburgh hospital in 1989[14] 10% of women either cancelled an appointment at some stage during the referral procedure, defaulted, or informed their doctor that they had decided to continue with the pregnancy. Arguably it is this group of women who require advice from a social worker rather than the great majority who are certain of their decision.

### Referral procedures

The mechanism by which a woman requesting abortion is referred to a gynaecologist varies widely throughout the UK. In many areas the referring doctor has to contact the gynaecologist personally, often a time consuming procedure. There are frequently long delays before a woman is seen by a gynaecologist and before the operation is done. In their study on late abortions in England and Wales[15] the RCOG reported that 45% of women operated on at between 13 and 16 weeks gestation had consulted their GP before 13 weeks. There have been improvements since 1985 and gradually the number of mid trimester abortions is falling (in 1989 over 80% of abortions were performed before 13 weeks). However, this is as a result of a reduction in the delay at all stages, including the stage of pregnancy at which women first present.

In their model specification the BCT recommend that women should be seen within 5 days of receipt of a letter of referral. One way to achieve this standard is to set up a centralised referral service as has been tried successfully in both Newcastle[16] and in Edinburgh.[14] In Edinburgh, gynaecologists reserve a specific number of appointments each week for termination referrals. The number is calculated to match the demand. A central agency holds all the appointments and offers the first available one to the referring doctor. Used for all referrals below 18 weeks gestation, this has significantly reduced the average wait for a referral from 11.2 days to 4.7 days in Edinburgh. The success of such a system depends on the continued commitment of the gynaecologists involved. It has been suggested that doing away with the need for two doctors agreeing to there being grounds for abortion may hasten the referral process. Unless women were able to refer themselves directly to the doctor performing the abortion this would not make any real difference to waiting times.

#### *Abortion procedure*

The BCT recommends that 95% of abortions should be performed within 5 working days of a woman being seen by the gynaecologist and that most should be done as day cases. In the UK the majority of abortions are still performed surgically. Availability of theatre time, gynaecological case load, emergency case load and individual consultant's policies all influence the speed with which any gynaecological patient reaches the operating theatre. There is no doubt that a commitment to providing an efficient service and the establishment of an efficient referral system helps. In Edinburgh the waiting time for

theatre fell in parallel with the wait for referral from 7 to 4 days. While gynaecological workload is increasing, changes in practice are altering the need for theatre time. Many units, for example, have replaced routine D & C under general anaesthesia with outpatient endometrial biopsy and the increasing use of minimally invasive surgical procedures will further reduce the need for both inpatient beds and, in some cases, operating theatre time.

It is surprising that of 54 health districts surveyed in the late 1980s and reported in 1990[17] the median figure for terminations performed as day case procedures was only 15%. Certainly admission as a day case makes life considerably easier for the patient.

Perhaps one of the most important developments with the potential to influence the wait for surgery is the introduction of a medical abortion service. RU486 (mifepristone) was granted a licence for use in medical termination of pregnancy in the UK in July 1991. In France where the treatment is only licensed for use up to 7 weeks gestation, 30% of terminations are now done using a combination of RU486 and prostaglandins (PG). For women suitable for medical abortion and where the service is offered, counselling for pregnancy termination should include a discussion of the advantages and disadvantages of medical versus surgical techniques.

Because of the current limitations on the availability of RU486 it is at present given on hospital premises, although this part of the procedure can be combined with the referral visit. Readmitted 48 h later, women stay in hospital for 6 h after PG administration. It is not necessary for them to be kept in bed or to wear night clothes or hospital gowns although beds must be available for women needing opiate analgesia or wishing to lie down.

In the UK the development of medical abortion services has been slow. By December 1991 only 35 units were purchasing RU486 (Roussel Uclaf – personal communication). Most Health Boards are facing a reduction in funding and some are burdened with a large financial deficit. Few have funding for so called 'developments' and the establishment of a medical abortion service is seen as such. Although medical termination of pregnancy removes the need for theatre time and, once set up, can be largely staffed by nurses, the organisation of a service requires commitment from managers and gynaecologists. The establishment of the service may require some funding or at least transfer of funds. Referrals still need to be seen and discussion of a choice of method – medical versus surgical – may lengthen the consultation. The 48 h gap between RU486 and prostaglandins limits the availability of the service to certain days of the week in most units and some effort has to be put into tracing women who default after taking RU486 but before receiving prostaglandins. At present follow-up to confirm that the abortion is complete is mandatory when medical methods are used to terminate pregnancy. Moreover, the cost of medical abortion at present is not significantly different from that of surgical techniques. In a recent letter to the British Medical Journal, Henshaw & Templeton[18] estimated the cost of a medical abortion at £400 compared with £480 for a surgical procedure. Nevertheless, medical abortion is an attractive option to many women and should be available throughout the UK. Only women referred early in gestation will be eligible for medical methods so that the potential for improving abortion services will only be realised in Health Authorities where an efficient referral service exists. The manufacturers of mifepristone, concerned about the dangers of misuse of the drug will only sell it to NHS hospitals or to other premises currently licensed to carry out abortions. Clause 37 of The Human Fertilisation and Embryology Act (1990) does allow the licensing of other types of premises to undertake abortions. With time it may become possible for family planning clinics to offer medical abortion or to make arrangements with a nearby hospital to share the load with the counselling, administration of RU486 and follow-up taking place in the Family Planning Clinic while the hospital provides the facilities for prostaglandin administration.

### Follow-up

Most gynaecologists do not see abortion patients after their discharge from hospital and follow-up is left – often only tacitly – to the referring doctor. Many women are given appointments at the time of the initial consultation with the GP and are usually seen 4–6 weeks after referral. Significant numbers fail to keep these appointments. It should be the policy of all hospitals and agencies discharging a woman after a termination of pregnancy to make sure that she leaves with sufficient and appropriate contraceptive supplies.

In addition to ensuring that the abortion is complete, the woman is free from side-effects and clear about her future contraceptive plans, post abortion consultations should give women the opportunity to discuss their feelings about the experience.

While more than 90% of women have no significant psychological problems following abortion a few will have difficulty coming to terms with their decision. If the referring doctor feels unable to help, many of the agencies such as the Brook Advisory Centre offer skilled counsellors.

1 in 5 women who have an abortion will have another at some stage in their life. Sensitive discussion of the reasons for becoming pregnant, failure of contraception and future intentions could go some way to reducing this figure.

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# The Establishment of a Centralised Referral Service Leads to Earlier Abortion

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**Summary**

**In 1988 a centralised referral service for termination of pregnancy was established in Edinburgh. This has led to a significant reduction in the time women who have requested termination wait to see a gynaecologist (mean 4.7 days) and in the time it takes before suction termination of pregnancy is undertaken (total wait 10.2 days). In 1988 only 40% of induced abortions in Edinburgh were carried out at 9 weeks gestation or before while in 1989 that figure had risen to 60%. In 1989 less than 10% of pregnancies were terminated at or after 12 weeks gestation, compared with 21% in 1988. Reasons for delays in obtaining an abortion are multifactorial but rapid referral once a woman has made the decision to seek help will be essential if she is to avail herself of the advantages of medical termination—only available until eight weeks of pregnancy.**

## Introduction

The number of terminations is rising annually throughout the United Kingdom. In 1989 in Scotland 10,159 pregnancies were terminated, a rate of 9.1 terminations per thousand women of reproductive age. While the mortality rate associated with therapeutic abortion has fallen—there have been no deaths from abortion in Scotland since 1981—major complications, haemorrhage, infection, operative trauma and thromboembolism, occur in over 2% of cases[1]. It is quite clear that the morbidity associated with the procedure increases with the gestation of the pregnancy at the time when it is terminated. The risk of major complications doubles when termination is carried out at 15 as compared with 8 weeks gestation[2].

Complete abortion can be induced medically in 97% of women with up to 56 days of amenorrhoea (8 weeks gestation) with a combination of an antiprogesterone (mifepristone) and a prostaglandin[3]. In France 30% of therapeutic abortions are now done using this method. Mifepristone is the subject of a current application for a product licence for use in the United Kingdom in early 1991 but only for the induction of abortion in women who are eight weeks pregnant or less at the time of termination.

While some women may take a long time to reach the decision to seek a termination of pregnancy, in many cases much of the responsibility for the delay lies with the medical

profession. There are frequently long delays before a woman is seen by a gynaecologist and again before the operation is actually done[4]. In their confidential study on late abortions in England and Wales, the Royal College of Obstetricians and Gynaecologists reported that 45% of women operated on at between 13 and 16 weeks gestation had consulted their General Practitioner (GP) before 13 weeks[5].

The establishment of a centralised service for the referral of termination requests has been shown to reduce significantly the delay between referral by the GP and the out-patient consultation[6]. Such a centralised abortion referral service was set up in Lothian in the latter half of 1988. In this paper we review the impact of the service on referral times and the mean gestation of termination of pregnancy in Lothian.

**Methods**

In 1988, 2,204 and in 1989, 2,210 pregnancies were terminated in the Lothian Region. While some 250 of these abortions were done in West Lothian the vast majority were undertaken in three main hospitals in Edinburgh. All the consultant gynaecologists working in these three hospitals agreed to participate in a centralised abortion referral service; the consultants in West Lothian wished to continue to operate their own local referral system. Each of 16 consultant gynaecologists working in the city of Edinburgh identified a number of out-patient appointments reserved exclusively for requests for termination of pregnancy. General practitioners and doctors at family planning clinics within the area wishing to refer for termination a women who is less than 18 weeks pregnant, telephone the Lothian Centralised Abortion Referral Service (LARS) which is based at the local family planning centre. The appointments clerk offers the first available appointment and at the end of the day contacts the out-patients' department at each of the three hospitals involved giving details of appointments issued. Termination appointment slots remaining unused twenty-four hours before the clinic may be used for other referrals. Referring doctors wishing to specify a particular hospital or consultant are offered the next appropriate appointment and some patients choose to delay, usually for domestic reasons. Doctors referring women beyond 18 weeks gestation or more contact the gynaecologist personally, as before. Referrals have been accepted through LARS since the first of November 1988.

All referrals through LARS to the Royal Infirmary of Edinburgh during the first six months of 1989 have been analysed to determine the mean waiting time between referral and consultation with a gynaecologist. By referring to ward operation books and individual patient's notes the waiting time between the out-patient consultation and operation has also been determined. Patients referred for a medical termination of pregnancy have been excluded from analysis and only women referred for a routine suction termination of pregnancy have been analysed. Data have been analysed using the Chi Square test of statistical significance.

In 1989, 2,262 women were referred through LARS requesting termination of pregnancy. Less than 2% of abortions are done privately in Scotland and we are confident that LARS handles at least 97% of termination referrals up to 18 weeks of gestation in Edinburgh.

**Results**

Mean waiting times between a woman being referred by her GP or other doctor for gynaecological consultation and between referral and the surgical procedure are shown in Table I. Requests for appointments have been subdivided into requests for a first trimester termination (< 12 weeks n = 507) and requests for a mid trimester termination (12–18 weeks n = 137). First trimester requests have been subdivided into those who took the first available appointment (n = 402) and those who, for some reason, chose to delay (n = 105). Only 29 women (7%) who took the first available appointment waited more than seven days before being seen by a gynaecologist and none waited longer than ten days. A total of 73% of women who were seen at the earliest available appointment underwent a suction termination of pregnancy within seven days of seeing the gynaecologist and only 11.7% waited more than ten days. Women who for some reason chose not to take the first available appointment waited slightly but not significantly longer to see a gynaecologist but did not have a longer wait for operation once they had been seen. Women referred for a mid trimester appointment passed through the system slightly more quickly than requests for first trimester termination—the median wait between the request for referral and initial consultation was nine as compared with 12 days.

**Table I: Mean Waiting Time Between Initial Consultation and Referral to the Gynaecology Clinic for Abortion and Between Initial Referral and Operation Among Patients Referred Via LARS to the RIE from 1 January–30 June 1989**

| *Appointment requested* | *n* | *Wait for referral (days)* | *Wait for operation (days)* | *Total wait (days)* |
|---|---|---|---|---|
| 1st trimester—first available | 402 | 4,7 ± 2.1 (range 1–10) | 5.6 ± 4.0 (range 0–23) | 10.2 ± 4.1 (range 1–23) median 12. |
| 1st trimester—delayed appointment | 105 | 5.5 ± 2.8 (range 1–19) | 5.6 ± 3.7 (range 0–20) | 10.8 ± 4.3 (range 1–22) median 12. |
| Midtrimester | 137 | 5.7 ± 3.0 (range 1–12) | 4.2 ± 3.1 (range 0–15) | 9.8 ± 4.2 (range 1–23) median 9. |

Referral times have been further analysed in a small subgroup of patients referred from Lothian Health Board community family planning clinics to the Royal Infirmary. Referral times during the first six months of 1989 are compared with the wait for referral during the first six months of 1988 before LARS was set up. Results are shown in Table II. Patients referred for pregnancy termination in 1988 waited significantly longer both for an appointment to see a gynaecologist ($p < 0.002$) and for operation ($p < 0.01$). In 1988 76% of women waited more than one week to be seen and 41% of them waited more than two weeks, while in 1989 over 85% of referrals were seen within one week and none waited more than ten days.

The percentage of pregnancy terminations undertaken in Lothian at each week of gestation from 5–22 weeks during 1988 until November when LARS came into operation and from its inception until the end of 1989 is shown in Figure 1. Before a centralised referral service was established just over 40% of terminations were being undertaken at nine weeks gestation or earlier and 21% at 12 weeks or later. During 1989, 60% of

**Table II: Mean Waiting Time Between Initial Consultation and Referral to the Gynaecology Clinic for Abortion and Between Initial Referral and Operation Among Patients Referred from Family Planning Clinics to the RIE from 1 January–30 June 1988 and 1989**

| *Appointment requested* | *n* | *Wait for referral (days)* | *Wait for operation (days)* | *Total wait (days)* |
|---|---|---|---|---|
| 1989— 1st trimester | 54 | 4.6 ± 2.9 (range 1–8) | 4.6 ± 3.4 (range 0–17) | 9.2 ± 3.3 (range 1–18) |
| 1989—Midtrimester | 17 | 6.4 ± 2.7 (range 1–12) | 4.9 ± 4.4 (range 0–14) | 11.3 ± 3.9 (range 1–14) |
| 1989—All | 71 | 5.3 ± 2.4 (range 1–12) | 4.9 ± 3.6 (range 0–17) | 10.1 ± 3.1 (range 1–17) |
| 1988—All | 88 | 11.2 ± 4.7 (range 0–21) | 6.8 ± 4.7 (range 0–20) | 18.0 ± 4.7 (range 0–20) |

pregnancy terminations were done at nine weeks or before and less than 10% of all terminations were done beyond 12 weeks gestation.

## Discussion

The introduction of a centralised abortion referral service in Edinburgh appears to have made a significant difference to the time women seeking pregnancy termination wait for referral to a gynaecologist—on average they wait one week less than they did before the service was set up. There has also been a significant decrease in the wait—having been seen by a gynaecologist—for the operation to be carried out. These improvements have led to a dramatic change in the average gestation at which termination of pregnancy is being performed in Lothian.

Other factors may have contributed to these changes. For some years now the Department of Obstetrics and Gynaecology in Edinburgh has been involved with research in medical methods of termination including the use of anti-progesterones. Women suitable for medical termination are often referred directly to the clinician involved—bypassing LARS. Equivalent numbers of medical terminations were done during 1988 and 1989 and they have been excluded from analysis. Knowledge of the availability of medical termination among both general practitioners and women seeking termination may have led to earlier referrals since the procedure is only suitable for women who are eight weeks pregnant or less. Increasing discussion in the media about abortion and the abortion law and changing attitudes towards abortion may make it easier for many women to confront the problem of an unwanted pregnancy sooner than they tended to in the past. These and other unrecognised factors may lead to earlier referrals.

The wait for operation during the period studied also appears to be shorter than it has been in the past. This may simply be a reflection of a better organised referral system leading to better organised operating lists. There is no evidence of a fall in the demand for other surgical gynaecological procedures to permit an improvement in the termination service, but it is possible that earmarking a number of out-patient appointments for termination referrals may make it more difficult to get an urgent appointment for other gynaecological problems such as post menopausal bleeding; this too may have an impact on the operating lists.

Women considering abortion occasionally change their minds during the referral procedure. Of the 735 women referred through LARS to the Royal Infirmary during the

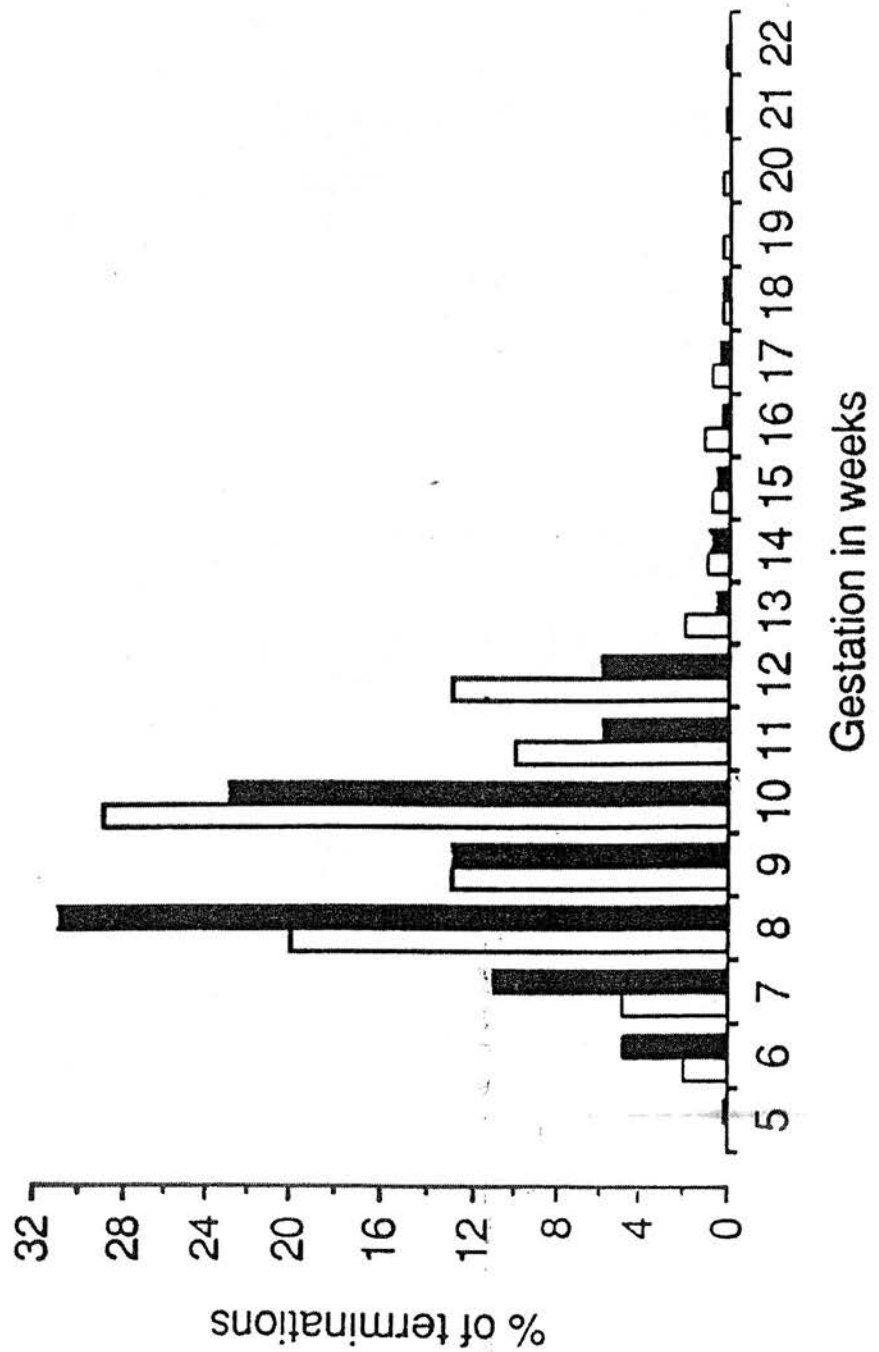


**Figure 1: Percentage of Terminations Being Undertaken in Lothian in Weeks of Gestation Before □ and After ■ LARS was Established. Scottish Health Service Information and Statistics Division (Used with permission).**

first six months of 1989 10% (73), either cancelled an appointment at some stage during the referral procedure (26), defaulted (31) or informed their doctor that they had decided to continue with the pregnancy (16). Too short a referral time may push some women into having an abortion which they may later regret. In France the law demands that there must be seven days between the doctor agreeing to terminate a pregnancy and actually doing so, in order to allow women time to reflect on the decision. However 16.6% (67) of the women taking the first available appointment to see a gynaecologist at the RIE had had the pregnancy terminated within six days of first consulting their GP; some would argue that this is too quick. Nevertheless if a significant number of women are to be able to take advantage of medical termination of pregnancy, they will have to decide to have an abortion within two weeks of missing a period in order to allow the system to cope. In many parts of the UK there appears to be no system and in England and Wales as a whole only 41% of abortions are carried out within the NHS, although a substantial further number are carried out with NHS funding on private premises. In Scotland, where less than 2% of abortions are done in the private sector, the need for a well organised community service is vital if termination of pregnancy is to be undertaken as early and therefore as safely as possible.

## Update

A product licence was obtained in June 1991 for the use of mifepristone (RU486) for termination of pregnancy up to 9 weeks gestation.

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# Multicentre criterion based audit of the management of induced abortion in Scotland

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Abstract

*Objectives*—To assess and improve the quality of care provided to women undergoing induced abortion.

*Design*—Two rounds of prospective, criterion based case note review audit.

*Setting*—Ten NHS gynaecology units throughout Scotland.

*Subjects*—2004 patient episodes of abortion care identified consecutively during two rounds of audit. The first round comprised 967 cases and the second round 1037.

*Interventions*—Dissemination of results from the first round of audit and recommendations for change in the form of a written report and at postgraduate meetings in participating hospitals.

*Main outcome measures*—Improvements in quality of care as assessed against 16 previously agreed criteria, both overall across the 10 study hospitals and within individual hospitals.

*Results*—Overall, four significant improvements occurred: increased availability of early medical abortion, decreased utilisation of surgical abortion at very early gestation, increased use of mifepristone priming before second trimester medical abortion, and increased provision of follow up. At the individual hospital level 42 of 150 elements of care studied were "close to optimal" at the time of the first round of audit, rising to 54 at the second round (NS). A total of 31 significant improvements in individual elements of care occurred, but 11 significant deteriorations also occurred (at the $P < 0.05$ level).

*Conclusions*—The prospective multicentre audit proved feasible and achieved the aims of any form of audit in terms of identifying deficiencies and variations in care. The audit results prompted objective review of local abortion services in participating hospitals. At least for some elements of care in some hospitals significant improvements were detectable.

## Introduction

Induced abortion is one of the commonest components of the Scottish NHS gynaecological workload, accounting for around 11 000 procedures per year.[1] Abortion care was therefore considered to be a particularly appropriate topic for medical audit and was recently addressed by means of a criterion based approach in the gynaecology audit project in Scotland.[2]

## Methods

A list of criteria for good quality care was agreed by a combination of objective review of contemporary medical publications, panel discussions, and postal survey of all consultant gynaecologists in Scotland (response rate 92%), as described.[3] The 16 criteria which were addressed in the multicentre audit are listed in the box.

Ten hospitals throughout Scotland representing 10 different health board areas and employing around half of all consultant gynaecologists in Scotland were included. During each of two audit periods an audit

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**Criteria for good quality care addressed in case note review audit and agreed among consultant gynaecologists in Scotland**

*Organisation of service*

- (1) All women requesting abortion should be offered appointment with gynaecologist within five days of referral
- (2) Induced abortion should be undertaken within seven days of appointment with gynaecologist
- (3) In absence of specific medical or social contraindications women undergoing abortion should be managed as day cases

*Preabortion investigations*

- (4) Woman's Rh status should be ascertained and Rh prophylaxis given after abortion if indicated
- (5) Gestation need not routinely be confirmed by ultrasound scan
- (6) Cervical smear history should be recorded for all women undergoing abortion
- (7) Women undergoing abortion should be screened for genital tract infection and treated if indicated

*Methods of abortion*

- (8) Women presenting early in pregnancy (<9 weeks' gestation) should have option of surgical or medical abortion
- (9) Suction termination should not be undertaken in very early pregnancy (≤6 weeks' gestation) because of high incidence of failure
- (10) In selected women undergoing surgical abortion, technique for cervical predilatation should be used
- (11) All surgical abortions at gestations >10 weeks should be carried out by experienced gynaecologist (post-MRCOG or equivalent)
- (12) For second trimester medical abortions pretreatment with mifepristone reduces induction abortion interval

*Postabortion care*

- (13) Before being discharged each patient should have agreed a contraceptive plan
- (14) Before being discharged each patient should be offered contraceptive supplies
- (15) A follow up appointment, either at hospital or with referring doctor, should be given to every patient
- (16) Follow up appointment should be within two weeks of abortion procedure

assistant (with a medical secretarial background) in each hospital identified all patients undergoing induced abortion. Mothers undergoing abortion because of fetal abnormality were excluded as they were thought to raise different care issues. Data relating to the agreed criteria were collected in a standardised manner in all 10 hospitals by transfer of information from case notes on to a review document. Each audit assistant was trained by the research fellow (GCP) in data transfer. Data from all hospitals were entered into a purpose designed database by using Paradox (Borland) software on an IBM compatible personal computer. Statistical significance testing by $\chi^2$ analysis (unless otherwise indicated) was performed with Instat 2 (Graphpad) software.

After the first audit period results and recommendations for change were disseminated as a written report mailed to all consultant gynaecologists. In addition, in seven of the 10 hospitals a postgraduate meeting was held, allowing a further opportunity to highlight local issues.

## Results

### CASES IDENTIFIED

A data collection period of six months (beginning in October 1992) was available for the first round of audit. It was planned to review 100 consecutive cases managed in each hospital during this time. In the larger hospitals 100 cases were identified during as little as six weeks, whereas in one of the smaller hospitals only 67 cases presented during the whole six months. Thus in total 967 cases were studied. Owing to constraints of the project timetable and funding, data collection for the second round of audit was restricted to a two month period (beginning in August 1993). All cases managed in each hospital during this time were identified and reviewed. The mean number of cases per hospital was 104 (range 20 to 266), and in total 1037 cases were studied.

### OVERALL IMPROVEMENTS

At the time of the second round of audit four significant overall improvements across the 10 hospitals were detected:

- The use of medical abortion for women at <9 weeks' gestation (criterion 8) rose from 39 to 516 (7·6%) to 172 of 541 (31·8%) ($P<0·0001$)
- The inappropriate use of surgical abortion in women at <7 weeks' gestation (criterion 9) decreased from 68 to 85 (80·0%) to 56 of 98 (57·1%) ($P=0·0017$)
- The use of mifepristone cervical priming before midtrimester medical abortion (criterion 12) increased from 15 of 64 women (23·4%) to 64 of 102 (62·7%) ($P<0·0001$)
- The recording of a follow up arrangement in the case notes (criterion 15) increased from 52% to 69% of cases (Wilcoxon signed rank test, $P=0·037$), and the advising of follow up within the recommended interval of two weeks after abortion also increased (from 5% to 32%; Wilcoxon signed rank test, $P=0·0645$).

There were no overall deteriorations in relation to any elements of care.

### IMPROVEMENTS IN INDIVIDUAL HOSPITALS

Fifteen of the agreed criteria were addressed on an individual basis in each of the 10 hospitals. (Criterion 9 was omitted in view of the small numbers of patients presenting at ≤6 weeks in any one hospital.) Thus 150 individual elements of care were assessed. Results from

TABLE I—*First round of audit. Results of individual hospitals in relation to 15 of agreed audit criteria*

| Criterion No | Element of care | Hospital No (No of cases studied) | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | | 1 (n=100) | 2 (n=100) | 3 (n=100) | 4 (n=100) | 5 (n=100) | 6 (n=100) | 7 (n=100) | 8 (n=100) | 9 (n=100) | 10 (n=67) |
| 1 | % Of cases seen within five days | 30 | 29 | 86 | 52 | 42 | 64 | 40 | 55 | 30 | 54 |
| 2 | % Of procedures done within seven days | 78 | 89 | 80 | 86 | 93* | 70 | 63 | 67 | 92* | 89 |
| 3 | % Of patients managed as day cases | 89 | 63 | 93* | 95* | 84 | 91* | 70 | 7 | 72 | 48 |
| 4 | % Of cases where Rh status was recorded | 95* | 99* | 98* | 100* | 98* | 99* | 100* | 86 | 94* | 97* |
| 5 | % Of cases having ultrasound scan | 33 | 46 | 17* | 17* | 25* | 37 | 97 | 83 | 13* | 9* |
| 6 | % Of cases where cervical smear history was recorded | 63 | 21 | 55 | 0 | 77 | 77 | 84 | 64 | 0 | 12 |
| 7 | % Of cases where genital tract swabs were taken | 92* | 14 | 2 | 1 | 2 | 88 | 15 | 1 | 0 | 0 |
| 8 | Early medical abortion service available (yes (Y), no (N)) | Y* | Y* | N | N | Y* | N | N | N | N | N |
| 10 | % Of high risk surgical abortions having predilatation | 61 | 69 | 25 | 71 | 92* | 10 | 13 | 62 | 10 | 87 |
| 11 | % Of surgical abortions at >10 weeks performed by senior registrar or above | 67 | 54 | 57 | 87 | 100* | 100* | 100* | 79 | 100* | 100* |
| 12 | Mifepristone used in second trimester medical abortion (yes (Y), no (N)) | Y* | Y* | N | N | N | N | N | N | N | N |
| 13 | % Of cases where contraceptive plan was recorded | 95* | 57 | 100* | 96* | 98* | 98* | 88 | 98* | 96* | 94* |
| 14 | % Of cases where contraceptive supplies were given by hospital | 20 | 16 | 43 | 24 | 83 | 20 | 16 | 12 | 80 | 81 |
| 15 | % Of cases where follow up arrangements were recorded | 74 | 25 | 100* | 99* | 91* | 7 | 37 | 55 | 26 | 6 |
| 16 | % Of cases where follow up within two weeks was advised | 13 | 4 | 18 | 0 | 1 | 3 | 0 | 4 | 6 | 0 |

*Asterisk indicates element of care where performance was "close to optimal."

TABLE II—*Second round of audit. Results of individual hospitals in relation to 15 of agreed audit criteria*

| Criterion No | Element of care | Hospital No (No of cases studied) | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | | 1 (n=266) | 2 (n=209) | 3 (n=149) | 4 (n=112) | 5 (n=49) | 6 (n=77) | 7 (n=81) | 8 (n=41) | 9 (n=33) | 10 (n=20) |
| 1 | % Of cases seen within five days | 66↑ | 26 | 89 | 17↓ | 33 | 29↓ | 53 | 49 | 67↑ | 5↓ |
| 2 | % Of procedures done within seven days | 78 | 86 | 84 | 77 | 75↓ | 75 | 75 | 73 | 85 | 80 |
| 3 | % Of patients managed as day cases | 85 | 82↑ | 96* | 86↓ | 94* | 90* | 72 | 27↑ | 82 | 65 |
| 4 | % Of cases where Rh status was recorded | 98* | 95* | 95* | 100* | 100* | 99* | 100* | 98* | 91* | 95* |
| 5 | % Of cases having ultrasound scan | 29 | 67↓ | 13* | 22* | 31 | 25* | 100 | 98↓ | 18* | 15* |
| 6 | % Of cases where cervical smear history was recorded | 81↑ | 10↓ | 38↓ | 99*↑ | 96*↑ | 70 | 76 | 80 | 51↑ | 55↑ |
| 7 | % Of cases where genital tract swabs were taken | 92* | 6 | 0 | 12 | 86↑ | 88 | 10 | 0 | 0 | 0 |
| 8 | Early medical abortion service available (yes (Y), no (N)) | Y* | Y* | Y*↑ | N | Y* | N | Y*↑ | N | N | N |
| 10 | % Of high risk surgical abortions having predilatation | 77 | 86 | 53 | 74 | 100* | 44↑ | 0 | 22 | 67 | 100* |
| 11 | % Of surgical abortions at > 10 weeks performed by senior registrar or above | 59 | 75 | 33 | 100* | 100* | 100* | 100* | 57 | 100* | 100* |
| 12 | Mifepristone used in second trimester medical abortion (yes (Y), no (N)) | Y* | Y* | Y*↑ | N | Y*↑ | Y*↑ | Y*↑ | N | N | N |
| 13 | % Of cases where contraceptive plan was recorded | 92* | 46 | 99* | 100* | 100* | 99* | 95* | 100* | 97* | 85 |
| 14 | % Of cases where contraceptive supplies were given by hospital | 42↓ | 6↓ | 52 | 44↑ | 96*↑ | 18 | 26 | 17 | 97*↑ | 50↓ |
| 15 | % Of cases where follow up arrangements were recorded | 89↑ | 52↑ | 94* | 100* | 98* | 14 | 80↑ | 98*↑ | 12 | 55↑ |
| 16 | % Of cases where follow up within two weeks was advised | 59↑ | 35↑ | 19 | 93*↑ | 2 | 0 | 2 | 66↑ | 3 | 40↑ |

*Asterisk indicates element of care where performance was "close to optimal." ↑Indicates significant improvement ($P < 0.05$). ↓Indicates significant deterioration ($P < 0.05$).

the first round of audit are summarised in table I. Of these 150 elements of care, 42 (28·0%) were judged to be "close to optimal" (arbitrarily defined as ≥ 90% of cases meeting the criterion, or (for criterion 5) ≤ 25% of cases undergoing ultrasound scanning, (for criteria 8 and 12) mifepristone being available).

Performance was particularly good in relation to recording of Rh status (nine hospitals achieved > 90%) and recording of patient's contraceptive plan (eight hospitals achieved > 90%). No hospital achieved close to optimal performance in relation to seeing patients within five days of referral, recording of cervical smear history, providing contraceptive supplies, or suggesting follow up within two weeks of the abortion.

The results from the second round of audit are summarised in table II. Fifty four elements of care (36·0%) were judged to be close to optimal. This increase over the first round failed to reach significance ($P = 0.1732$). However, major improvements occurred in relation to 31 individual elements of care. These comprised the introduction of a new service (either early medical abortion or the use of mifepristone for second trimester medical abortion) in six instances or significant ($P < 0.05$) improvements in the proportion of cases meeting a given criterion in 25 instances. The most common significant improvements were in relation to recording of cervical smear history, recording of a follow up plan, and advising early follow up (each occurred in five hospitals).

Eleven significant deteriorations in the proportion of cases meeting a given criterion also occurred. The most common deterioration was in relation to the proportion of cases seen by a gynaecologist within five days of referral (three hospitals).

There was no significant difference between the number of improvements occurring in the seven hospitals in which a postgraduate meeting was held (23 improvements out of a possible 105) and the three hospitals in which results and recommendations were disseminated as a report only (eight out of a possible 45) ($P = 0.6632$).

## Discussion

The multicentre audit proved feasible and achieved good cooperation among gynaecologists. While acknowledging the theoretical advantages of clinical rather than medical audit we perceived that this project engendered a strong sense of ownership as a result of being a confidential single discipline exercise initiated by the Scottish branch of the Royal College of Obstetricians and Gynaecologists, of which all participants were members.

The first round of audit enabled variations and deficiencies in care to be identified and undoubtedly prompted open and objective discussions about local abortion services in participating hospitals. It might be argued that some of the changes detected in the second round were unrelated to the audit feedback exercise. However, one of the most dramatic improvements (the increase in mifepristone priming before midtrimester abortion) occurred at a time unrelated to new publications on the topic and before the granting of a product licence. Medical audit can never be the sole stimulus to change; it acts alongside other educational initiatives. In this instance, however, we believe the audit was instrumental in changing practice.

It is clear that in order to maximise the benefits from the national investment in clinical audit attention must be directed at identifying the most effective strategies for disseminating audit results and for implementing change. Russell and Grimshaw have provided suggestions for the effective dissemination and implementation of clinical practice guidelines[4] (to which audit recommendations are closely related).[5] They suggest that dissemination is best accomplished by "specific educational intervention" rather than simply "mailing targeted groups." However, in this study no more improvements occurred in those hospitals where a postgraduate meeting was held specifically to address the audit findings than in those where a postal report only was provided.

Implementation entails encouraging clinicians to adopt the audit recommendations. The only implementation strategy employed in this study was fore-

### Clinical implications

- The quality of care provided to women requesting abortion was assessed by means of criterion based audit in hospitals throughout Scotland
- Deficiencies in care and variations among hospitals were detected
- Participating clinicians responded to the audit results and to recommendations made by the audit team
- Medical audit can act along with other educational initiatives in increasing awareness of effective treatments and in providing a stimulus to change
- This audit exercise prompted open and objective discussions among clinicians about many aspects of patient care and is believed to have been instrumental in stimulating significant changes in relation to some

warning participants that a second round of audit was imminent. A more effective strategy might have been to incorporate recommendations in a structured patient record document for use while managing abortion referrals, a technique which has proved successful in implementing guidelines for the management of infertility.[6]

The modest success of this national audit has confirmed an interest and willingness to participate in medical audit among Scottish gynaecologists. Refinements in audit methodology are required to translate this good will into substantial improvements in patient care.

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# Agreeing criteria for audit of the management of induced abortion: an approach by national consensus survey

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**Abstract**

***Objective*—To obtain a national consensus view of suggested criteria for good quality care in induced abortion to serve as a basis for standards for audit to assess current clinical practice.**

***Design*—Postal, questionnaire survey assessing consensus agreement with criteria identified from a literature review and refined by an invited panel of four gynaecologists and the gynaecology audit project in Scotland (GAPS) committee.**

***Setting*—Scotland.**

***Subjects*—All 132 practising consultant gynaecologists.**

***Main measures*—Overall level of agreement with each of 20 suggested audit criteria.**

***Results*—121 completed questionnaires were received (response rate 92%), of which 119 were returned in time for analysis; 107 came from consultants who practised abortion routinely and were included in the analysis. Nineteen of 20 suggested criteria were validated by an overall balance of agreement. The most strongly supported criterion (agreement score +93) was for ascertaining rhesus status of the woman and prophylaxis after abortion, if indicated. The only criterion to elicit a negative agreement score (–27) was that dilatation and evacuation is the best method of abortion at 12–15 weeks' gestation. The ranked and prioritised criteria resulting from this exercise are being used within a national audit project.**

***Conclusions*—A postal questionnaire survey among interested clinicians resulted in a good response rate and enabled the audit criteria to be validated and ranked more objectively and among more clinicians, than would have been possible by group discussion.**

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## Introduction

Criterion based audit has been described as offering a valuable and realistic method of audit based on review of medical records.[1–3] In this approach key elements of clinical management (audit criteria) are agreed by participating clinicians. Case notes can then be reviewed by non-medical audit assistants who extract selected data relating to the agreed criteria. Shaw suggested that around 15 such criteria can be addressed in a single audit.[1]

The practical difficulties of establishing audit criteria acceptable to all participating clinicians are acknowledged,[2] and it has been suggested that criteria should be based on the findings of a literature review combined with discussion by the audit group. Discussion by all participating clinicians is clearly impractical for large scale audit projects undertaken regionally or nationally. This paper describes an approach to agreeing audit criteria, incorporating a postal questionnaire survey of all involved clinicians, which has been developed and used successfully in a national audit project.

The gynaecology audit project in Scotland (GAPS) was initiated by the Scottish Executive Committee of the Royal College of Obstetricians and Gynaecologists with the aim of auditing three topics (induced abortion, endometriosis, and carcinoma of the vulva) nationally. The audit of each topic is seen as an end in itself, but, in addition, the project as a whole is seen as an opportunity to develop approaches to the methodology of audit which can be applied subsequently to further topics.

The approach to establishing audit criteria which has been developed within this project is described with reference to the first topic, induced abortion.

## Methods

A review of contemporary medical literature relating to the management of induced abortion provided the basis for a provisional list of statements, or criteria, which were seen as summarising essential elements of good quality care. The criteria covered four, previously agreed broad areas of abortion care: organisation of the service, investigations before abortion, methods of abortion, and care after abortion.

For example, *Criterion 1 – Women requesting induced abortion should be offered an appointment with a gynaecologist within five days of referral.*

This criterion was taken from the Birth Control Trust model service specification[4] which provided the basis for several of the suggested criteria under the "organisation of the service" heading. The provisional list of criteria was then modified and refined by means of discussions with two separate groups of clinicians: an invited panel of four

gynaecologists (two with a special interest in abortion care and two generalists) and also the GAPS steering committee.

A questionnaire was then designed to assess "level of agreement" with each of 20 criteria in the final list. Respondents were asked: "The following list of statements relating to the management of induced abortion has been drawn up following a literature review and discussion with a panel of clinicians. We would like you to indicate your level of agreement with each statement as representing *an important criterion for good quality care* on a 5 point scale graded as follows: 1 strongly agree, 2 agree, 3 neither agree nor disagree, 4 disagree, or 5 strongly disagree."

In September 1992 the questionnaire was sent to all 132 consultant gynaecologists practising in Scotland. The mailing list was based on names and addresses provided by the college and updated by means of telephone inquiry to all 26 gynaecology units in Scotland. A second copy of the questionnaire, with a letter of reminder, was sent to those consultants who had not responded within two weeks. Data from the questionnaires were entered into a purpose designed database using Paradox (Borland) software on an IBM compatible personal computer.

Each criterion was allocated an "agreement score" in order to convey the overall balance of agreement with each criterion among consultants. In allocating the agreement scores each response of "strongly agree" scored +2, "agree" +1, "neutral" 0, "disagree" −1, and "strongly disagree" −2. The scores for each criterion were then summed and expressed as a percentage of the maximum possible score had all consultants strongly agreed (that is, of 204) to give the final "agreement score". Thus, any positive score indicates a balance of agreement, +100 is the maximum possible score and −100 is the minimum possible score.

## Results

As a result of the two mailings, 121 completed questionnaires were eventually received (a response rate of 92%), 119 in time for analysis. Of the 119 respondents, 12 indicated that they never accepted abortion referrals and answered no further questions. Thus, the opinions on abortion care of those 107 respondents who manage induced abortion in the course of their routine practice were used to validate the audit criteria.

The table shows all 20 criteria, in summary form, ranked according to the agreement score allocated to each. The agreement scores represent an attempt to indicate the *balance* of agreement with each criterion, giving additional weighting to responses of *strongly*

*Suggested criteria for good quality abortion care ranked by level of agreement among 107 Scottish consultants*

| *Ranking* | *Agreement score (Possible score +100 to −100)* | *Consultants who agreed or strongly agreed (%)* | *Abbreviated criterion* |
|---|---|---|---|
| 1 | +93 | 100 | Rhesus status should be determined before abortion |
| 2 | +69 | 95 | Cervical predilatation indicated for selected patients |
| 3 | +61 | 90 | Surgical abortion at gestation >11 weeks requires an experienced operator (beyond member of Royal College of Obstetricians and Gynaecologists or equivalent) |
| 4 | +60 | 88 | If indicated, oral contraception should begin immediately after abortion |
| 5 | +59 | 87 | Surgical abortion should be managed on a day case basis |
| 6 | +58 | 82 | Contraceptive advice and supplies should be provided after abortion |
| 7 | +56 | 83 | Advice on "emergency contraception" should be provided after abortion |
| 8 | +51 | 79 | The "appointment to abortion" interval should be ≤7 days |
| 9 | +50 | 81 | The "referral to appointment" interval should be ≤5 days |
| 10 | +44 | 68 | There should be a policy for treating potential genital tract infection |
| 11 | +43 | 80 | Routine ultrasonography is unnecessary before abortion |
| 12 | +41 | 78 | "Induction to abortion" interval should be <24 hours at >15 weeks' gestation |
| 13 | +40 | 72 | Abortion patients should begin cervical screening regardless of age |
| 14 | +39 | 74 | Surgical evacuation should not be routine after medical abortion |
| 15 | +34 | 63 | Women at <9 weeks' gestation should have a choice of surgical/medical abortion |
| 16 | +25 | 40 | Mifepristone reduces the induction to abortion interval in the 2nd trimester |
| 17 | +23 | 59 | All abortion patients should be offered a follow up appointment |
| 18 | +14 | 41 | Surgical abortion should be avoided at gestations <6 weeks |
| 19 | +6 | 33 | The follow up appointment should be within 14 days of the abortion |
| 20 | −27 | 19 | At gestations of 12–15 weeks dilatation and evacuation is the method of choice |

agree or disagree. The percentage of respondents who agreed or strongly agreed with each criterion is also shown. Nineteen of the 20 suggested criteria gained positive agreement scores, indicating an overall balance of agreement. However, the ranked criteria may be viewed as forming a range in terms of their agreement scores and thus in terms of the importance that can be attached to them as a basis for acceptable audit standards against which current practice may be judged and towards which clinicians might aspire.

The most strongly supported criterion, with an agreement score of 93 out of a theoretical maximum of 100 was: *The woman's rhesus status should be ascertained and Rh prophylaxis given after the abortion if indicated.* All respondents agreed with this criterion, almost 85% *strongly* agreed. This fundamental component of abortion care is clearly acceptable to all as a target to be met in providing an abortion service.

Among the least strongly supported of those criteria gaining positive scores were those relating to follow up after abortion. *A follow up appointment, either at the hospital, or with the referring doctor, should be given to every patient* was ranked only 17 out of 20, and less than 60% of respondents agreed with it. *The follow up appointment should be within 14 days of the abortion* was ranked 19/20; only a third of respondents actively agreed with it, most felt "neutral". Thus, although the Birth Control Trust and also the Scottish Home and Health Department's Study Group on the management of gynaecological services emphasise that the abortion service should encompass such aftercare,[4 5] these criteria were not given high priority by Scottish consultants.

Only one of the suggested criteria gained a negative agreement score (–27): *At gestations of 12–15 weeks surgical abortion (dilatation and evacuation) is the method of choice.* This criterion is well supported by results from large series of patients managed in the United States[6 7] but is clearly not acceptable in Scotland at present as a criterion for good quality care.

## Discussion

The results of the national survey have enabled us to produce a list of criteria, ranked according to their relative importance to Scottish gynaecologists. It seems reasonable to regard the 19 statements for which there was an overall balance of agreement as valid criteria for audit against which to measure current practice. This process is currently underway in the form of a prospective, case note review audit of induced abortion in 10 representative hospitals throughout Scotland.

The ranking of the criteria according to their relative importance will enable those aspects of care which fail to measure up to the criteria to be similarly ranked. This will be helpful in deciding which aspects of care warrant change and in prioritising such changes for the allocation of resources. For example, if it were found in the course of prospective audit that the rhesus status of abortion patients was not being routinely measured, then participating clinicians, who judged this to be of fundamental importance would be expected to give high priority to implementing change in this aspect of care whereas this would not be so if it were found that abortion patients were not routinely being given follow up appointments within 14 days of their procedure.

For aspects of care (such as follow up arrangements) in which the views of "specialists" in abortion care[4 5 8] differ from those of the generality of consultants, the low ranking of relevant criteria serves to highlight appropriate topics for educational initiatives. For such aspects of care opinion must be changed before there can be hope of changing practice. In this study the views of consultant gynaecologists have been used to estimate the relative importance of different aspects of abortion care. Consultants seem to rank "technical" aspects of care more highly than the "supportive" aspects such as follow up. Other interested groups such as nursing staff and consumers might have ranked the different elements of care differently.

This approach to establishing audit criteria could be applied to other topics by surveying clinicians on a geographical basis, as was done here, or by surveying the membership of specialist professional groups and societies with regard to more specialised topics.

The survey described was undertaken to establish criteria for audit rather than to develop formal clinical practice guidelines. However, a recent working group document from the Scottish Home and Health Department has highlighted the close relation between audit and development of guidelines (Clinical Resource and Audit Group, 1992, unpublished), and the consensus approach used here could appropriately be applied to the validation of guidelines and local protocols.

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# Impact of the introduction of new medical methods on therapeutic abortions at the Royal Infirmary of Edinburgh

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**Objective** To assess the impact of the introduction of new medical methods on the provision of therapeutic abortions at the Royal Infirmary Edinburgh.

**Design** A review of the total number of abortions performed by medical and surgical means between 1989 and 1995 (inclusive); a prospective survey of the terminations of pregnancy (≤ 9 weeks of gestation) performed over the six-month period of January to June 1994; and a questionnaire of the reasons why women chose a particular method.

**Setting** Large teaching hospital in Scotland.

**Subjects** One thousand and seven women seeking early pregnancy termination between January and June 1994.

**Main outcome measures** Proportion of pregnancies terminated by medical means; comparison of complete abortion rate, incidence of complications and morbidity following both medical and surgical methods (≤ 9 weeks of gestation); reasons for preference of the method of abortion.

**Results** Since 1991 there has been a progressive increase in the number of medical abortions performed at the Royal Infirmary of Edinburgh, and by 1994 the majority of women (57%) seeking abortion at ≤ 9 weeks chose a medical method. Women who chose medical abortion had more years at full-time education and were less likely to smoke ($P < 0{\cdot}04$). Both medical and surgical methods were highly effective (> 96% complete abortion) with a low incidence of complications and morbidity. However, women who had chosen the medical method were less likely to receive antibiotics for suspected endometritis than their surgical counterparts ($\chi^2$, $P = 0{\cdot}0001$).

**Conclusions** If this trend towards medical methods in Edinburgh is repeated elsewhere, it will inevitably have an impact on gynaecological services by releasing staff and operating time for other purposes.

## INTRODUCTION

Unwanted pregnancy is a universal phenomenon which occurs in all societies irrespective of their religious beliefs and cultural background. Even in Scotland where there is relatively easy access to free contraception, unwanted pregnancy resulted in 10 in 1000 women of reproductive age having a legally induced abortion in 1993[1]. Vacuum aspiration is one of the most common gynaecological procedures performed in the UK and can account for a substantial proportion of a gynaecologist's operative workload. Modern techniques of vacuum aspiration, including priming agents which facilitate cervical dilatation, have made a contribution to the overall safety and efficacy of this method so that major morbidity occurs in < 1% of cases, and the complete abortion rate approaches 98%[2–4]. The development of non-surgical methods of inducing an abortion, however, eliminates the requirement for an operation and anaesthesia and in addition the success of the method is not dependent on the skill of a surgeon. In July 1991 the antiprogestin mifepristone (RU 486) (Hoechst-Roussel Ltd, Uxbridge, Middlesex, UK) was granted a licence in the UK for the purpose of inducing a medical abortion in the first nine weeks of pregnancy. In combination with a suitable prostaglandin analogue, it has been shown to be an effective and safe alternative to vacuum aspiration[5,6]. Although this method is reported to be acceptable to women as a means of terminating a pregnancy[7–9], it has not as yet been widely adopted in the UK. A survey of all Scottish Consultant Gynaecologists

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undertaken in September 1992 revealed that only half of the gynaecology units in Scotland offered such a medical abortion service[10]. The reasons for its relatively low use include a lack of awareness that this method exists, the misconception that it has a low efficacy and, in addition, the conditions imposed by the Department of Health may make its provision, at least in the private sector, actually more expensive than vacuum aspiration[11].

The Royal Infirmary of Edinburgh is a major teaching hospital which has offered a medical abortion service for the termination of early pregnancy since July 1991 when mifepristone was licensed for use in the UK. In 1993, 69% of all abortions and 84% of medical abortions (≤ 9 weeks) in Edinburgh and the surrounding district (Lothian) were performed at the Royal Infirmary[1]. The purpose of this study was to assess the impact that new medical methods have made on the provision of therapeutic abortions at the Royal Infirmary of Edinburgh. This was assessed by determining 1. the numbers of abortions performed by medical and surgical means since 1989; 2. the numbers of women (≤ 9 weeks of gestation) choosing a medical method and their reasons for doing so; 3. comparing the efficacy, complications and morbidity associated with both medical and surgical methods (≤ 9 weeks).

## METHODS

The number of vacuum aspirations and medical abortions performed each year at the Royal Infirmary of Edinburgh between 1989 and 1995 was obtained from the log books of the Gynaecology Operating Theatre and the Medical Abortion Unit, respectively. The figures obtained with this method agreed to within 5% with the official hospital statistics for each year. Since each type of gynaecological procedure performed at the hospital is given a specific code number, the latter statistics were easily obtained from the hospital computer database from the code for 'termination of pregnancy'.

A detailed prospective study of all terminations of pregnancy performed in the Royal Infirmary was carried out over the six month period of January to June 1994. Although one aim of the study was to determine the total number of abortions and the gestations at which they were performed, the main aim was to compare the efficacy, complications and morbidity associated with both medical and surgical methods of inducing an abortion up to 9 weeks of gestation. Approval for the project was obtained from the local Ethical Subcommittee. Termination of pregnancy was carried out under the conditions of the United Kingdom 1967 Abortion Act.

Since 1993 most women in Lothian have been given a standard information sheet when they attend their general practitioners or family planning doctors requesting a termination of a pregnancy (≤ 9 weeks amenorrhoea)[12]. This information sheet has been approved by the hospital medical and nursing staff and describes in simple terms the medical and surgical methods used to terminate a pregnancy, the conditions for being suitable for a medical abortion and the symptoms likely to be experienced after both procedures. Thus women who are suitable for either method can consider the merits of both procedures before referral to the hospital. After further counselling with the gynaecologist, women of ≤ 9 weeks amenorrhoea, if medically suitable, are offered a choice between medical abortion and vacuum aspiration. An endocervical swab is routinely taken at this visit to screen for chlamydial infection. Women who have positive swabs are treated with appropriate antibiotics on the day of the abortion procedure and contact tracing of partners is arranged.

Throughout the study period women (≤ 9 weeks of gestation) who chose a medical abortion were given 200 mg mifepristone orally (Mifegyne, Hoechst-Roussel Laboratories Ltd, Uxbridge, Middlesex, UK) and returned 36 h to 48 h later to the Medical Abortion Unit to receive the prostaglandin analogue[13]. The prostaglandin analogue used was either half (0·5 mg) of a gemeprost vaginal pessary (Cervagem, Farillon, Romford, Essex, UK) or 600 μg oral misoprostol (Cytotec, Searle, High Wycombe, Bucks, UK). Women remained in the unit for 4 h under the supervision of nursing staff. A vaginal examination was performed prior to discharge to determine if fetal tissue had been passed and a follow up appointment was arranged for two weeks later. Vacuum aspiration was almost always performed as an outpatient procedure under general anaesthesia. Nulliparous women routinely received cervical preparation by inserting a 1 mg gemeprost vaginal pessary into the vagina 3 h before surgery. Vacuum aspiration was also the method used to terminate pregnancies between 9 and 12 weeks of gestation. A minority of pregnancies between 12 and 14 weeks were also evacuated surgically after cervical priming with a gemeprost vaginal pessary, as described above. The majority of women of more than 12 weeks of gestation, however, had an abortion induced medically with 200 mg of oral mifepristone followed 36 h later by a gemeprost pessary (0·5 mg or 1 mg) every 6 h[14].

The gestations at which all abortions were performed were derived from the case notes and were calculated on the basis of menstrual history and pelvic examination, or pelvic ultrasound if the clinical findings were uncertain. For the purposes of the morbidity

study, however, data was collected prospectively on all women (≤ 63 days amenorrhoea) undergoing a medical abortion ($n$ = 329) or a vacuum aspiration ($n$ = 215) performed as a day case procedure. A further 31 surgical abortions (≤ 9 weeks of gestation) were performed in other locations within the hospital during this time and so were excluded from the detailed prospective study. Information regarding patient characteristics, parity, past medical history and details of the abortion procedure was recorded on pre-tested data sheets on the day of admission to hospital. Information on the morbidity following each method was collected at a follow up appointment two weeks later by one of the investigators. This appointment was given to all the women who had a medical abortion ($n$ = 329) and to all the women who had a vacuum aspiration and lived within Lothian ($n$ = 194). At this visit, women were questioned about the severity of vaginal bleeding, complaints related to the abortion procedure and whether they had sought medical advice or required treatment following discharge from hospital. When women failed to attend for follow up on two occasions, the general practitioner or referring doctor was contacted by postal questionnaire to ascertain whether the patient had any significant morbidity relating to the abortion procedure and if so what treatment was required. Data were thus available on the wellbeing of all those in the study who had a medical abortion and 96% of those who had a surgical abortion. In addition, the hospital admissions computerised database was searched to determine whether any woman who had defaulted from follow up had been readmitted to the Royal Infirmary within four weeks of the procedure and the circumstances for admission.

Throughout the study period, a questionnaire was also conducted to determine the factors which influence a woman's decision to choose a particular abortion method. Women seeking a termination of pregnancy (≤ 63 days amenorrhoea) ($n$ = 207) were invited prior to vacuum aspiration ($n$ = 103) or administration of mifepristone ($n$ = 104) to complete a questionnaire which consisted mainly of a series of questions with answers which required women to intimate their response by placing a pencil mark in a box alongside the most appropriate answer. Because of the pressure of work it was not possible to ask every woman who presented to complete the questionnaire which was given to up to five women per day until the desired number had been obtained. Eighty-six of 103 women seeking vacuum aspiration and 90 of 104 women who had a medical abortion completed the additional section of the questionnaire which contained several open ended questions asking women to state their reasons for choosing a particular method.

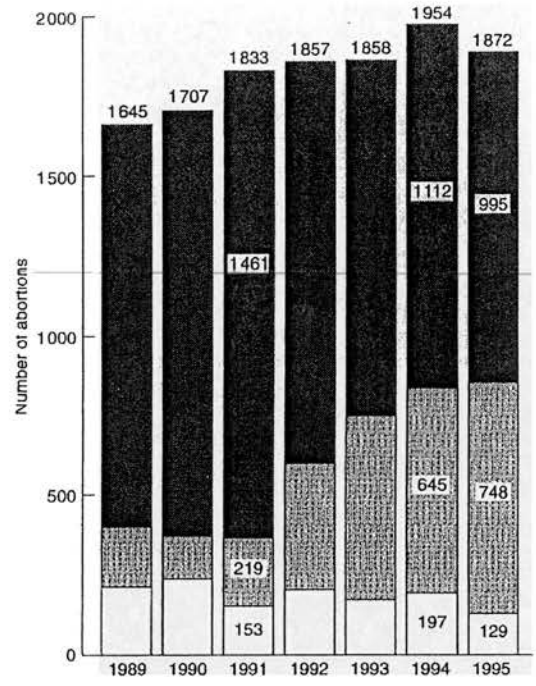


**Fig. 1.** The number of abortions performed in the Royal Infirmary of Edinburgh from 1989 to 1995. Mifepristone was licensed in Great Britain for induction of abortion in July 1991. ■ = surgical; ▨ = medical ≤ 9 weeks; □ = medical > 12 weeks.

### Statistical analysis

For the purpose of statistical analysis a $\chi^2$ test of significance was used to compare data between groups.

## RESULTS

The total number of abortions performed in the Royal Infirmary rose slightly from 1,645 in 1989 to 1,872 in 1995 (Fig. 1). Since 1991 when mifepristone was licensed for use in the medical termination of early pregnancy, the number of first trimester abortions induced using medical methods increased annually from 219 in 1991 to 748 in 1995. The small number of medical abortions in early pregnancy performed prior to 1991 were conducted as part of clinical research studies with mifepristone. Since new medical methods were introduced, the total number of vacuum aspirations performed has decreased and by 1995 represented only 53% of the total. The number of mid-trimester abortions induced medically (> 12 weeks of gestation) have remained fairly constant at about 200 per year until 1995 when the number fell to 129.

Over the six-month period of more detailed study (January to June 1994) a total of 1007 terminations of

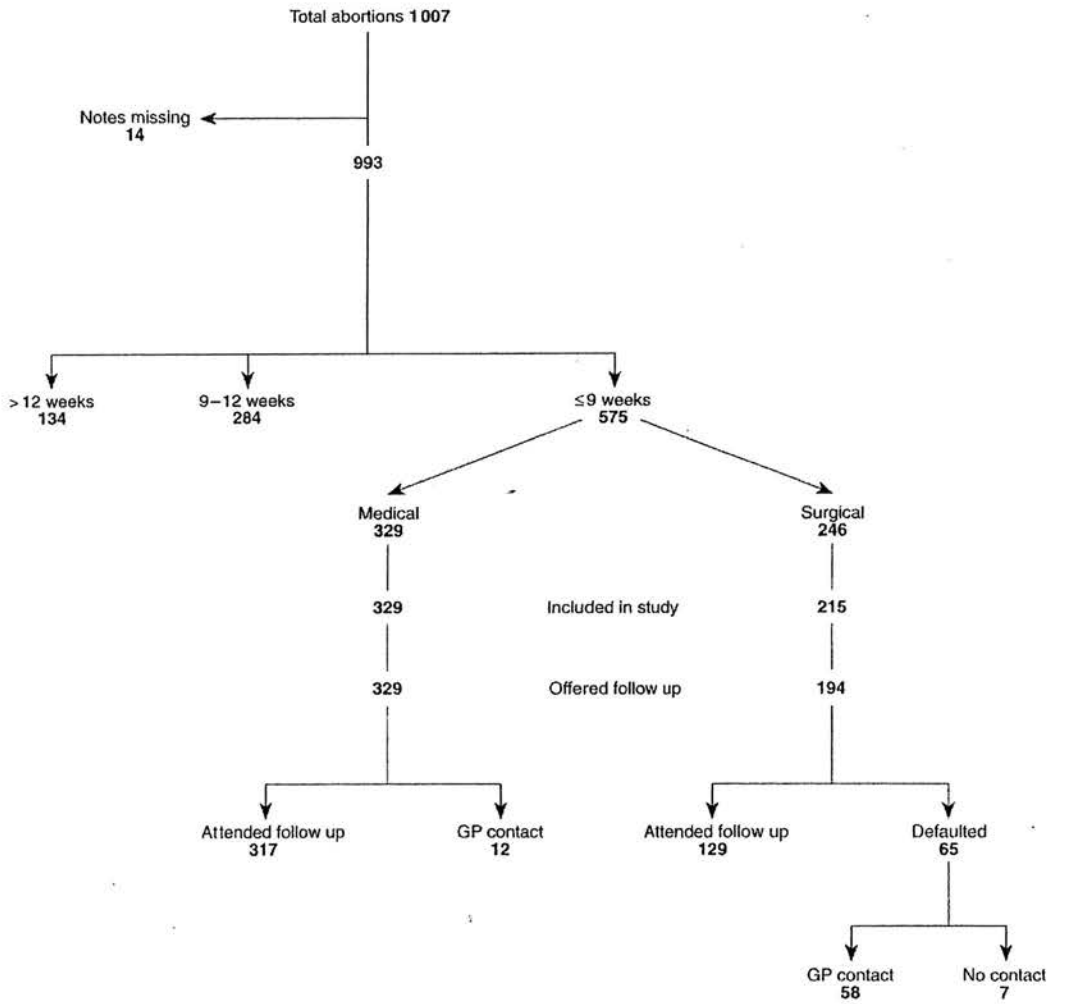


**Fig. 2.** Numbers of women undergoing medical and surgical methods of abortion at the Royal Infirmary of Edinburgh between January and June 1994 and numbers of those attending follow up as part of detailed prospective study.

pregnancy were performed at the Royal Infirmary (Fig. 2). In 14 women case notes were missing and so the gestation at which these abortions were performed could not be determined. Of the remaining 993 induced abortions, 13% were > 12 weeks; 29% were 9 to 12 weeks and 58% were ≤ 9 weeks of gestation. The majority of pregnancies > 12 weeks of gestation were terminated by medical means (83%, $n = 111$), with the remainder terminated by vacuum aspiration. All terminations between 9 and 12 weeks of gestation were performed using vacuum aspiration. Of the 575 women ≤ 9 weeks of gestation, 329 (57%) chose to have the pregnancy terminated by the medical method (Fig. 2). These women were of similar ages, marital status and parity to those undergoing vacuum aspiration, but were more likely to be nonsmokers ($\chi^2 = 4{\cdot}5$, $P < 0{\cdot}04$) and to have a higher level of education ($\chi^2 = 8{\cdot}6$, $P < 0{\cdot}04$) (Table 1). In addition, a higher proportion of women who chose medical abortion had previously had an induced abortion (32·5% and 24% for medical and surgical, respectively; $\chi^2 = 4{\cdot}4$, $P < 0{\cdot}04$). The incidence of chlamydial infection was similar in both groups (~5%) and all women were known to have received appropriate antibiotic therapy on the day of the abortion procedure.

Table 1. Characteristics of women (≤ 9 weeks of gestation) choosing medical and surgical methods of abortion. Values for characteristics are given as *n* / total (%) except for mean age which is shown as years ± SEM.

| Characteristics | Medical $n = 329$ | Vacuum aspiration $n = 215$ |
|---|---|---|
| Mean age | 25·5 ± 0·3 | 25·3 ± 0·5 |
| Single status | 230/329 (70) | 135/213 (63) |
| Primigravidae | 220/329 (67) | 130/215 (60·5) |
| Previous induced abortion | 107/329 (32·5)* | 52/215 (24) |
| Nonsmoker | 187/310 (60)* | 101/199 (51) |
| Finished education ≥ 19 years | 56/308 (18·5)* | 22/174 (13) |

*Difference from vacuum aspiration $P < 0·04$.

The efficacy of medical and surgical methods (≤ 9 weeks of gestation) were similar with complete abortion rates of 96·4% and 97·9%, respectively. Four women (2·1%) following vacuum aspiration and five (1·5%) following medical abortion required further surgical evacuation of the uterus because of retained products of conception. In addition seven women (2·1%) had vacuum aspiration of the uterus to terminate an ongoing pregnancy following attempted medical abortion. There was one woman in whom it was suspected that the uterus had been perforated during vacuum aspiration (≤ 9 weeks of gestation) but this was not confirmed at subsequent laparoscopy. The incidence of complications following both methods was low. Complications arising from the medical method consisted of two cases of persistent heavy bleeding after prostaglandin administration, which required the uterus to be evacuated. There was also one case of a drug-induced skin eruption following mifepristone (erythematous macular rash on upper body) which resolved spontaneously.

At the follow up visit, we wished to assess the incidence of post-abortal pelvic infection and blood loss as indices of morbidity. Of those women who were offered a follow up appointment, 129 (67%) from the surgical group and 317 (96%) from the medical group attended. A greater proportion of women who had undergone vacuum aspiration had already sought medical advice in the interim from their general practitioner or referring doctor for complaints related to the abortion procedure [18 (14%) and 11 (3%) of the women in both groups, respectively; $\chi^2 = 16·6$, $P = 0·0001$]. Although we were unable to assess the true incidence of pelvic infection, we were able to use the information from the referring doctors to determine the use of antibiotics for suspected endometritis. Women who had undergone vacuum aspiration (≤ 9 weeks of gestation) received antibiotics for suspected endometritis more frequently than their medical counterparts [18/187 (9·6%) and 4/329 (1·2%), respectively; $\chi^2 = 20·6$, $P = 0·0001$]. Subjective blood loss after the abortion was assessed by asking women in whom bleeding had ceased by the follow up visit [116 (90%) in the surgical and 176 (55%) in the medical group] to describe how the entire episode of bleeding compared with their normal menses. Bleeding was more often reported as 'heavier than normal menses' after a medical [117 (66%)] than after a surgical abortion [13 (11%); $\chi^2 = 134·9$, $P = 0·001$].

Women who completed questionnaires were representative of all the women in the prospective audit with respect to age, marital status and parity. Most women stated that they were first aware that a medical method existed when they made professional contact with the referring doctor [43 (41%) and 52 (51%) of those undergoing surgical and medical methods, respectively] and most had already decided on their preferred method of abortion before the consultation with the hospital gynaecologist [60 (59%) and 75 (74%) of the surgical and medical groups, respectively]. Women in both groups agreed that the two most important sources of information regarding the methods used were medical staff [$n = 174$ (87%)] and the information sheet [$n = 80$ (40%)]. All the women having a medical abortion had been offered a choice of method, but 13 of the women having a vacuum aspiration (13%) had not been offered a choice due to the presence of a pre-existing medical condition (such as asthma) which constitutes a contraindication to prostaglandins. Most women expressed a definite preference for their chosen method and only a small number (six in each group) stated that the decision had virtually been based on the result of 'tossing a coin'.

The majority of women completed the section in the questionnaire containing open-ended questions on their reasons for their choice of method (Tables 2 and 3). While many women chose a medical abortion in order to avoid surgery or anaesthesia, those who preferred vacuum aspiration did so because they wished to be unconscious and unaware of the procedure, since they felt they would be distressed at the prospect of seeing the products of conception. In contrast some of the women chose the medical method because they felt it to be 'more natural' and would allow them to remain 'in control' of the process.

## DISCUSSION

Despite ready access to free contraceptive advice from both general practitioners and a network of family planning clinics, the number of unwanted pregnancies terminated annually by abortion has not fallen during the period surveyed (1989–1995) in Lothian or Scotland (over 2000 and 11,000, respectively)[1].

**Table 2.** Vacuum aspiration: main reasons for preference. Values are given as *n* (%).The total is more than 100% due to the fact that some women stated more than one reason for preference.

| Reason | *n* = 86 |
|---|---|
| Only single visit required | 34 (40) |
| Unconscious and unaware of procedure | 34 (40) |
| Quicker completion of abortion | 25 (29) |
| Distress at prospect of seeing products of conception | 22 (26) |
| Perceived higher failure rate of medical method | 13 (15) |
| Perceived more common method | 10 (12) |
| Possible side-effects of drugs used in medical method | 3 (4) |

**Table 3.** Medical method: main reasons for preference. Values are given as *n* (%). The total is more than 100% due to the fact that a few women stated more than one reason for preference.

| Reason | *n* = 90 |
|---|---|
| Avoid anaesthesia | 32 (36) |
| Avoid surgery | 30 (33) |
| More natural | 22 (16) |
| In control | 10 (11) |
| Future infertility after vacuum aspiration. | 6 (8) |

Part of the continued demand can be explained by demographic changes as the young women born during the baby boom of the 1960s pass through their period of maximum reproductive activity[15]. In our study throughout this period there has been a gradual increase in the proportion of women requesting abortion at an earlier gestation and in the Royal Infirmary the majority of pregnancies (58%) are now terminated before the ninth week of gestation. Since new medical methods of inducing abortion were introduced in 1991 the number of women requesting this method has increased annually, representing by 1994 the majority (57%) of pregnancies under nine weeks. Including those pregnancies in the mid-trimester, 45% of all abortions in the Royal Infirmary are now terminated medically. As the complication rate of abortion is related to gestation, it is desirable that the pregnancy be terminated at the earliest possible gestation. If women seeking an abortion are to be given a choice of method, an efficient system ensuring speedy referral from general practitioner to gynaecologist, such as exists in Edinburgh, is necessary[16].

Our results, demonstrating that the majority of women opt for medical abortion if given a choice, are similar to a study of French women[7]. The main reasons for choosing the medical method are to avoid surgery and anaesthesia or because it is perceived to be a more natural experience[9]. A small number of women in our survey stated that they would prefer this method because it puts them, rather than the surgeon, in 'control' of the procedure. In agreement with the results of others[9] we found that some women request vacuum aspiration because they wish to be unaware of the abortion procedure or because the abortion is completed quickly and only requires one visit to hospital. It has previously been reported that women who live at a distance from the hospital tend to prefer vacuum aspiration as a method of abortion[9], which may explain why almost one-third of the women who were offered a follow up appointment after vacuum aspiration failed to attend.

Women who chose a medical abortion had more years of full-time education and were less likely to smoke, suggesting that, as in France, women choosing medical methods tend to be of a higher socio-economic status[7]. The reason for this difference is uncertain but may be related to the fact that they have a greater ability to understand fully the choices available and seek medical advice at an early stage. In contrast to previous studies[7,9] we found that women choosing the medical method were more likely to have had a previous induced abortion than those who chose the surgical method. The reason for this is unclear, but one possibility is that having had a previous abortion, they may recognise the symptoms of pregnancy at an early stage and seek termination of an unwanted pregnancy without delay. Thus, having presented at an earlier gestation they can avail themselves of the option of a medical abortion. Since most women decided on the preferred method of abortion after consultation with the referring doctor, it would appear that the initial abortion counselling exerts a major influence on the woman's choice of method. It is therefore important that general practitioners and family planning doctors remain well informed of all aspects of treatment including new developments. As the information sheets were shown to be a valuable source of information for helping women decide upon the preferred method of abortion, it is appropriate that they are provided at this early stage of the abortion counselling.

Both methods of abortion were shown to be highly effective. The cases of ongoing pregnancy following medical abortion during the study period occurred as part of a larger randomised study comparing the efficacy of different prostaglandins, which confirmed previous suspicions that oral misoprostol is less effective than gemeprost when used at gestations of 50 to 63 days[13,17].

The results of the detailed prospective study demonstrated that both medical and surgical methods of abortion have a low incidence of complications. An interesting finding, however, was that women

who had a surgical abortion received antibiotics for suspected endometritis eight times more often than their medical counterparts. Similar findings have also been observed among women who expressed no preference for a particular abortion method and were randomly allocated to either vacuum aspiration or medical abortion[18]. A lower incidence of infection might be expected following a medical abortion since this method is noninvasive, involves no instrumentation and thus there is a lower likelihood of pathogens being introduced into the uterine cavity. It is also possible that the medical method may confer protection against ascending infection through the pharmacological effects of mifepristone. Previous animal studies have demonstrated an increase in leucocytes in the antiprogestin-treated pregnant cervix[19], and it is therefore possible that this could enhance local immunological defences against infecting organisms. However, women who chose vacuum aspiration attended follow up less often than their medical counterparts and had often seen a doctor in the interim and commenced antimicrobial therapy. Thus the increased use of antibiotics in this study may to an extent reflect different practitioners' prescribing policies. It is also possible that the higher incidence of use of antibiotics following vacuum aspiration could be due to the fact that women with complications would be more likely to attend the hospital for follow up. This seems unlikely, however, because there was no difference in the use of antibiotics in those women who attended for follow up at the hospital (13/129) compared with those who defaulted but were treated by their general practitioner (5/58).

Although subjective blood loss was greater following the medical method, we have previously demonstrated in a quantitative study that the actual blood volume lost (~80 mL) following both methods is similar[20]. The difference between the objective or measured blood loss and the subjective or reported blood loss is likely to be accounted for by the fact that with a surgical abortion most of the blood is lost at the time of vacuum aspiration, whereas blood loss occurs more gradually following a medical abortion.

This study demonstrated that the introduction of new medical methods of inducing an abortion has made a significant impact on the clinical services involved in providing therapeutic abortions at the Royal Infirmary of Edinburgh. Not only has it given women a choice of abortion method where none previously existed, but medical abortion has proved to be the more popular method which is both safe, effective and highly acceptable as a means of terminating an early pregnancy. In addition, the reduced demand for vacuum aspirations has inevitably served to release operating theatre time for other gynaecological procedures to be performed. If this trend towards medical methods continues and is repeated in other gynaecological units throughout the country, it will have important implications for the provision of abortion services nationwide.

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# Patients' Views on Abortion Care in Scottish Hospitals

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## Abstract

**This paper summarises the views on their care of 688 women undergoing induced abortion in 10 Scottish hospitals. Over 80% were satisfied with care provided by medical and other staff and 75% felt they had received enough emotional support. Hospital staff discussed contraception with 92% but offered contraceptive supplies to only 54%. Only 24% of patients eligible for early medical abortion were offered a choice of methods and only 44% of all patients were offered any form of follow-up, although 83% felt follow-up was worthwhile. Over a quarter of women reported health problems in the month following abortion. These women could not be predicted on the basis of age, gestation, parity or method of abortion. Significant differences among study hospitals were measurable in relation to satisfaction with care by nursing and ancillary staff, perceptions of emotional support and provision of contraceptive advice and supplies. Better care appeared to be provided where women were managed in a special abortion unit rather than where care was integrated into the general gynaecology workload.**

## Introduction

Induced abortion is the second most common procedure in the Scottish NHS gynaecological workload, accounting for 12% of inpatient plus day case discharges (around 11,000 procedures per year).[1] In view of its numerical importance, abortion care may be considered a particularly appropriate topic for medical audit and was included among three topics addressed by the Gynaecology Audit Project in Scotland (GAPS).

In 1983, the NHS Management Inquiry[2] emphasised the importance of eliciting the views and experiences of NHS users and subsequent discussions as to how the quality of health care should be measured have included patient satisfaction as an important dimension.[3,4] However, most surveys which followed the Management Inquiry initiative were managerially led and focused on 'hotel' aspects of hospital care rather than clinical treatment.

The GAPS audit of abortion care included a postal questionnaire survey of patients, seeking their views on various elements of their clinical management. The results of the survey are presented in this paper.

## Method

Ten hospitals throughout Scotland were recruited into the audit. These comprised a mixture of teaching and district general hospitals, large hospitals and small and represented 10 different Health Board areas. Thus, the participating hospitals represent almost the full spectrum of settings in which NHS gynaecological care is delivered in Scotland and employ around half of all consultant gynaecologists.

Consecutive women undergoing induced abortion were identified in all 10 hospitals during two audit periods (during 1992 and 1993) and their case notes reviewed as described elsewhere.[5] Each patient was asked by ward staff if she was willing to participate in a survey about her care. A questionnaire was sent to the home address of each consenting patient four weeks post-abortion. The questionnaire addressed the following topics:

1. General satisfaction with care provided by doctors and by other hospital staff.
2. Provision of emotional support.
3. Provision of contraceptive advice and supplies.
4. Views on the availability of a choice of abortion methods and of follow-up.
5. Post-abortion health problems.

Completed questionnaires were returned (using a S.A.E. provided) to the project office where data were entered into a purpose-designed database using Paradox (Borland) software on an IBM-compatible PC. Statistical significance testing (using the chi squared or t tests as appropriate) was performed using SPSSPC software.

## Results

*Response.* A total of 2,002 patients were identified in the course of the audit exercise. Of these, 1,073 (54%) consented to participate in the patient survey and were sent a questionnaire. A total of 688 completed questionnaires were returned, a response rate of 64% of those who consented to participate and 34% of the total.

Responders have been compared with non-responders in terms of age, gestation, parity and method of abortion. Responders were slightly older (mean age 26.0, SD 6.8 years vs 24.7, SD 6.3 years; $p < 0.001$); were less likely to be primigravidae (270 of 688 [40%] vs 604 of 1,325 [46%]; $p = 0.028$) and were more likely to have undergone surgical rather than

medical abortion (574 of 688 [86%] vs 1,028 of 1,325 [78%]; $p < 0.001$). There was no significant difference in gestation between responders and non-responders.

*General Satisfaction.* Patients were asked to indicate their level of satisfaction with care provided by doctors and by nursing and ancillary staff on a five-point scale ranging from 'very satisfied' to 'very dissatisfied'. Responses are summarised in Figures 1 and 2. Overall, more patients were 'satisfied' or 'very satisfied' with care by nursing and ancillary staff than with care by doctors (604 [88%] vs 569 [82%]; $p = 0.008$). There were no significant differences among the 10 hospitals in the percentage of patients satisfied with care by doctors (range 73% to 91%; chi squared test, $p = 0.543$). However there were

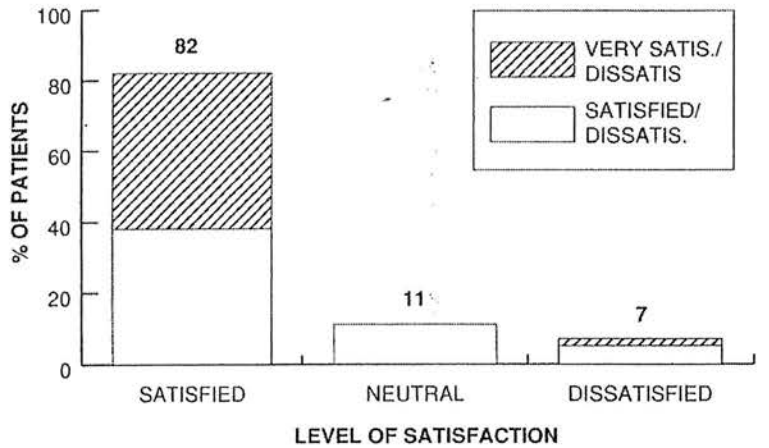


**Figure 1. Overall Satisfaction with Care Provided by Doctors**

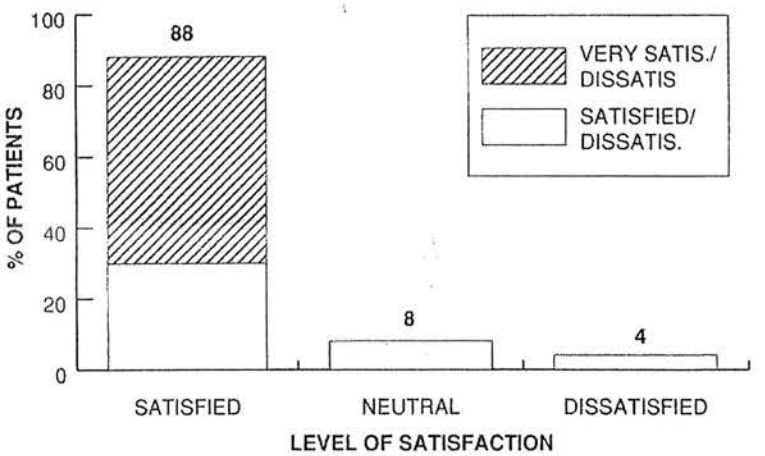


**Figure 2. Overall Satisfaction with Care Provided by Nursing and Ancillary Staff**

significant differences in satisfaction with care by nursing and ancillary staff (range 70% to 99%; chi squared test, $p < 0.001$).

*Provision of Emotional Support.* Patients were asked three questions in an attempt to assess the adequacy of counselling and emotional support. Responses are summarised in Table I. There were significant differences among the 10 study hospitals in relation to the percentage answering 'yes' to question 3, relating to overall perception of emotional support (range 57% to 93%; chi squared test, $p < 0.001$).

**Table I: Patients Responses Related to Counselling and Emotional Support**

| *Question* | *No.* | *Patient Answering 'Yes'* *%* |
|---|---|---|
| 1. During your clinic appointments, did you have enough time and help in reaching your decision to have an abortion? | 592 | 86 |
| 2. Do you feel now that your decision was right for you? | 613 | 91 |
| 3. Overall, do you feel that you received enough emotional support from the hospital staff during your clinic visits and hospital treatment? | 502 | 75 |

*Contraceptive Provision.* Patients were asked if hospital staff had discussed contraception and if they had offered to provide contraceptive supplies. Of 675 patients who answered these questions, 619 (92%) indicated that contraception had been discussed and 364 (54%) that supplies had been offered. Again, there were significant differences among hospitals: 'contraception discussed' ranged from 78% to 100% ($p < 0.001$) and 'supplies offered' ranged from 22% to 90% ($p < 0.001$).

Patients were further asked: 'What are you doing about contraception just now?' Of 684 who answered, 589 (86%) had adopted a contraceptive method at four weeks post abortion (the pill in 55%). Forty women (6%) responded that they 'did not need contraception just now' and 55 (8%) that they were 'using nothing but planned to start soon'.

Women were also asked if they were aware of the availability of emergency contraception. Of 682 who answered, 504 (74%) answered 'yes'.

*Choice of Methods.* Gestation data were available for 668 respondents. Of these, 346 (52%) were < 9 weeks gestation when first seen at the hospital and were potentially eligible for early medical abortion. Of these, 84 (24%) indicated that they had been offered a choice of method and 45 of these (54%) had undergone a medical procedure.

Of the 84 women who were offered a choice, 74 (88%) felt that 'being offered a choice was good', only five (6%) felt that the choice 'made things more complicated' and a further five were 'uncertain'.

*Follow-up.* Patients were asked if a follow-up visit either at the hospital or with the (referring doctor) had been arranged for them. Of 681 who answered, 385 (56%) were offered no follow-up. Where follow-up was arranged, it was with the general practitioner in most cases (203; 69%). Women were also asked if they felt a follow-up appointment was worthwhile. Of 618 who answered, 511 (83%) answered 'yes'.

*Post-Abortion Health Problems.* Women were asked: 'In the last month, since your abortion, have you had any health problems connected with your treatment?' Of 681 who answered, 181 (27%) indicated that they had experienced a total of 257 problems. The problems described are summarised in Table II.

**Table II: Post-Abortion Health Problems Described by 181 Patients**

| *Problem* | *No. of patients* |
|---|---|
| Excess bleeding | 88 |
| Excess pain | 54 |
| Infection/discharge | 48 |
| Depression | 22 |
| Required re-evacuation | 17 |
| Miscellaneous | 28 |
| **Total** | **257** |

Those responders who reported health problems have been compared with those who did not in terms of age, gestation, parity and method of abortion. There were no significant differences between the two groups in relation to any of these factors.

## Discussion

The response rate to this survey was (not unexpectedly) low at 64% of those who agreed to participate. Many patients were reluctant to receive questionnaires sent to their home addresses and the need to obtain written consent produced some administrative difficulties for ward staff. However, responders did not differ greatly from non-responders in terms of age, gestation, parity or method of abortion and may be viewed as fairly representative of women undergoing abortion in Scottish NHS hospitals.

It is reassuring that, in general, women seem very satisfied with care by doctors and, even more so, by other hospital staff. It is, however, disappointing that a quarter of patients felt they had not received enough emotional support from hospital staff although in the 'best' hospital 93% were satisfied with this aspect of care.

National recommendations advocate that abortion care should include contraceptive provision and the prevention of further abortions.[6-8] It is disappointing, therefore, that

almost half of the patients indicated that they were not offered contraceptive supplies by hospital staff. Again, in the 'best' hospital, 90% were offered supplies. It is reassuring that the vast majority of women had obtained a contraceptive method from some source and had adopted it at 4 weeks post-abortion. Only a small group appeared to have an unmet need for contraception.

National guidelines also advocate that abortion services should encompass aftercare[7] but almost half of the patients indicated that they had been offered no follow-up. It was not possible to identify those patients who experienced post-abortion health problems on the basis of age, gestation, parity or method of abortion and, therefore, it appears that the opportunity for follow-up should be offered to all.

Abortion care is offered in a variety of settings in the 10 study hospitals. In some, abortion patients are integrated into general gynaecology clinics and wards whereas, in others, the patients are managed in clinics and wards dedicated to abortion care. In this survey, significant differences among hospitals were measurable in relation to satisfaction with care by nursing and ancillary staff, perception of emotional support provided and discussion and provision of contraception. In each instance, the best results occurred in hospitals where women are managed in abortion-dedicated clinics or wards.

Thus, the multicentre survey revealed that, in general, abortion patients are satisfied with their care but there is scope for improvement in terms of provision of emotional support, availability of a choice of abortion methods, provision of contraceptive supplies and follow-up. Abortion care may be best provided in units dedicated to this purpose.

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# Modern Methods of Inducing Abortion

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# 7 Counselling for Abortion

*Anna Glasier*

## The counselling process

In many countries abortion is common. In the UK a woman's lifetime chance of having an abortion is around one in 40, while presently in the USA one in four recognized pregnancies ends in induced abortion. Nevertheless, the decision to have a pregnancy terminated is never an easy one. A multitude of personal feelings and emotions have to be taken into account and even when abortion may seem to be the only option the decision is never a simple process of logical evaluation. In recognition of the difficulties most women face in making the decision, specific counselling for women seeking abortion is available in many countries. In the USA shortly after abortion was legalized in all states in 1973 a new profession—abortion counsellor—was created [1]. Some states have no laws regulating abortion counselling; others have strict informed consent laws detailing precisely what information must be given to women considering abortion [2]. In the UK, the Committee on the Working of the Abortion Act (the Lane Committee) reporting in 1974—some 7 years after legalization of abortion—recommended that every woman should have the opportunity of adequate counselling before making the decision to have her pregnancy terminated [3]. In some countries abortion counselling is mandatory.

Counselling has become a rather fashionable term and much value is placed on the concept by laypeople. Despite its popularity there is no standard definition of counselling and the term means different things to different people. The then Department of Health and Social Security in England in a circular published in 1977 described abortion counselling as, 'providing opportunities for discussion, information, explanation and advice' in a manner which is both 'non-judgemental and non-directional' [4]. In Britain, most women are 'counselled' by one or more of the professionals involved in the process of arranging and carrying out the abortion; the majority, however, do not see a professional counsellor. But, whoever does the counselling and however it is done, every woman





should ideally feel that she has had an opportunity to explore her feelings and anxieties and to make an informed choice. She may be sad about the decision she has had to make but should have no long-term regrets.

Professionals who counsel women about abortion usually cover three areas: (i) decision-making; (ii) information provision: and (iii) emotional support.

### *Decision-making*

Most women faced with an unplanned pregnancy, even if they had taken no precautions to prevent it, are surprised or shocked to find themselves pregnant. Allen, in her book *Counselling Services for Sterilisation, Vasectomy and Termination of Pregnancy* [5], describes a series of in-depth interviews of 231 women who had just undergone induced abortion between 1982 and 1983 in the UK. Of the women interviewed, 56% knew immediately they suspected a pregnancy that they wanted an abortion, only 16% initially wanted to continue with the pregnancy, 10% were undecided and 11% did not know what to do.

Most women discuss their situation with their partner, a relative or friend before consulting a doctor and when they do consult their minds are made up. Even if they are quite certain of their decision these informal discussions often serve to confirm it. In Allen's study [5], conversations with partners were the most important influence in helping women to make the decision. Young women—particularly teenagers—sometimes talk to their mothers but often to girlfriends who are perceived to be particularly helpful because they are female, of a similar age and know the woman personally. Allen also interviewed a substantial number of professionals involved in counselling for abortion. Most professionals involved with counselling see the decision-making process as being of fundamental importance. They want to encourage the woman to think of both the practical and emotional consequences of all the possible options: abortion, continuing with the pregnancy and adoption. They are particularly concerned that unless a woman is quite certain of her decision she will be more likely to regret it later. A small number of women will need more time and perhaps more counselling to help them to make up their minds. The decision may, ironically, be more difficult for teenagers who can sometimes feel caught in the middle if their family and perhaps the partner's family become involved in the deliberations.

Some women do change their minds. In a small survey in Edinburgh [6], 10% of women who had been seen by at least one doctor and referred

to the gynaecologist failed to keep their appointment at some stage during the process. Some left it to the last minute and simply did not turn up for the operation. Many women are afraid that they may be refused an abortion and perhaps for some it is not possible to make the final decision until they are quite certain that they really do have a choice. For others, the reality of abortion may not become apparent until they are faced with the practicalities of attending for surgery and find that at the last minute they cannot go through with it. In some countries such as France, statute demands a waiting period between the time the abortion has been agreed and the time it is carried out to allow women the opportunity to reflect on their decision free from the worry that the request may be refused. Last minute changes of mind may cause particular problems with first-trimester medical abortion where the 48-h delay between the antiprogesterone and the prostaglandin treatment allows time for a change of heart.

In the UK every woman seeking an abortion must see two doctors, both of whom must sign a form stating that there are legitimate grounds for terminating the pregnancy. Most women see their general practitioner (GP) first and then a gynaecologist who provides the second signature and performs the abortion. Professionals involved with abortion often feel that the GP is the best person to counsel the woman as he or she is most likely to know her and her personal circumstances. Some women, however, prefer to see a doctor who does not know them—this applies particularly to teenagers and married women whose pregnancy may be the result of an extramarital relationship. These women may attend a community family planning clinic (although not all clinics are able to make direct referral to gynaecologists), or they may, for reasons of perceived privacy, choose to go privately, thus having to pay for the abortion. The majority of women do not attend the doctor for help with making the decision (only 12% did so in the Allen study [5]) or for emotional support (only 3%). Seeing a doctor is a necessary part of getting an abortion and women attend expecting a pregnancy test, information and referral. In order to satisfy themselves that there are grounds for termination most doctors and counsellors discuss the reasons why the pregnancy is unwanted and the practical and emotional consequences of all the options: abortion, continuing with the pregnancy and keeping the baby and adoption. Most usually explore whether the woman is absolutely certain about her decision since uncertainty may be more likely to lead to regret. By the time they see the second doctor most women are certain that they want an abortion and few expect help with decision-making from the gynaecologist. Since the gynaecologist also has to satisfy himself or herself that there are legitimate grounds for the abortion, he or she usually explores the same areas of discussion. Some women find these inevitable questions personal and intrusive; they do not expect to discuss the reasons, merely the details. Others feel that they have to 'make the case' to the gynaecologist for having their pregnancy terminated.

Allen concluded from her study that in the 1980s abortion counselling in the UK was 'patchy' [5]. In the USA, women receive more counselling in non-profit-making clinics than in those which are profit making [2]. Not all doctors are sympathetic and often the counselling depends more on the personality of the doctor than on the circumstances of the woman. Young unmarried women are less likely to be treated sympathetically and women who have had one or more abortions in the past may even be treated punitively. Women who are seen to have conceived because of a true method failure, such as an intrauterine contraceptive device (IUCD) failure, are more likely to receive a sympathetic hearing. Many women suspect intuitively that this may be the case and some will claim method failure even when they have not been using contraception.

Some women also see either a social worker or someone specifically trained in abortion counselling. In the UK, this is more likely to be the case in private agencies such as the British Pregnancy Advisory Service or Brook Advisory Centres. Although these professionals may often be seen to be particularly helpful—perhaps because they have more time—most women feel that they do not need to see a social worker or psychiatrist. In the Allen study [5], 28% of women were seen by a medical social worker, most thought that it was a waste of time and only one-quarter of them found the discussion helpful. In the UK, it is rare for a woman to be referred to a social worker—indeed, the need for such referral may be greater among those women who decide to continue with their pregnancy.

As discussed above, most women have made their decision long before they see a doctor and they see no need for prolonged discussions. The skill of the counsellor lies in the ability to detect those women who do need lengthy discussions and more support and those who may be at risk of severe regret. In Allen's study, only 7% of women felt that they had not had enough counselling. When asked what they wanted most women felt that abortion should be quicker and easier to obtain—they wanted information, understanding and emotional support, but most of all they wanted the abortion.

### *Information provision*

Women perceive doctors involved in the counselling process more as a source of information than as a source of help with decision-making or

emotional support. The information that doctors want to give and that the women want to receive may not always be the same. Most women want to know, in varying degrees of detail, what happens when a pregnancy is terminated. In the UK, France and Sweden women who present early enough may have a choice of medical or surgical abortion. Clinicians should discuss the different techniques together with their advantages and disadvantages, to enable a choice to be made. Doctors want to discuss the risks and side effects of abortion and both parties may be concerned with the question of the effect of abortion on future fertility. The information should be realistic, non-biased and apolitical. In some states in North America, the information that is given is sometimes designed to be off-putting with graphic—and sometimes pictorial—descriptions of fetal development.

The women who were interviewed in Allen's study felt they would have liked more information about abortion before they 'got into the system' [5]. An explanatory leaflet available from GPs and family planning doctors, which the woman can keep, is very helpful. Women also need information about what happens after the abortion, the expected duration of bleeding, how soon intercourse is permitted, even such details as when to have a bath. This is probably best given after the procedure, perhaps by nursing staff, and a separate information leaflet may be more sensitive.

Counsellors and particularly doctors regard discussion about contraception as being a vital part of the counselling process. In a Scottish study [7], 119 consultant gynaecologists strongly agreed that contraceptive advice should be given after the abortion. Interestingly, they did not think that all abortion patients should be offered a follow-up appointment with either themselves or the referring doctor. In the Allen study, most consultants discussed future contraception with the woman but few gave much information. Future contraceptive plans are usually discussed before the abortion is carried out. This may not be the best time. A woman who is anxious about being pregnant and worried that her request for an abortion may be denied, may not be receptive to a detailed discussion about contraception. Frequently, the decision to have a termination arises because a relationship has ended and the woman may not see an immediate need for future contraception. Some younger women are so devastated by the unwanted pregnancy that their reaction to any discussion of the future is to swear that they plan never to have intercourse again. While a discussion about future contraception prior to or even immediately after the abortion may not be ideal, in some cases it may be the only chance the professional has. Even if a follow-up appointment is given after the abortion many patients default.



### *Emotional support*

Counselling for abortion should provide emotional support. For most women, abortion is emotionally painful. The decision and the procedure may cause sadness but it should not cause regret. Although many women having an abortion will receive emotional support from their families or friends, good professional counselling at the time of the decision can be extremely helpful and can reduce the psychological trauma of abortion. Women who are well counselled usually feel less guilty, less depressed, less isolated and at the time of the procedure they also feel less pain. In a study of patients undergoing first-trimester medical abortion in Edinburgh [8], women were admitted to a hospital bed in a single room or to a shared sitting room or hospital ward with a number of others undergoing the same experience. Treatment in small groups enabled women to share their experiences and they felt the benefit of this kind of supportive companionship. In France, some centres now recommend treatment in small groups for this reason [9].

### *Post-abortion counselling*

While most women experience a huge sense of relief after an unwanted pregnancy has been terminated and many studies have demonstrated a significant improvement in psychological well-being after compared with before abortion [10], a small number do have difficulty in coming to terms with having an abortion. In the USA [2], it is estimated that 20% of women suffer from severe feelings of loss, grief and regret. These feelings may progress to anger (at herself and at her partner), or to depression and even obsession. These feelings are more likely to arise in women who: lack social support; whose decision to terminate the pregnancy is in conflict with their family or their religious beliefs; who feel they were pressurized into having an abortion; who have abortion because of fetal anomaly; and who are very young or have a very late abortion. Some women may need prolonged counselling by trained experts, although many find that a few sessions of post-abortion counselling allows them to come to terms with their emotions.

## Template for services

The worldwide trend towards the liberalization of abortion laws which started in Europe in the 1930s has continued over the last decade. Some 63% of the world's population live in countries where abortion is either

available on request or where social factors can be an indication [11]. However, 25% of women still have access to abortion only if pregnancy is life-threatening. Liberalization of the abortion laws leads to but does not guarantee a safe abortion service. In most countries in which abortion is legal only licensed medical personnel provide it, although the policies and practices regarding the setting vary widely.

In many developed countries, there is a move away from the provision of abortion within a hospital setting. For example, in the Netherlands, Norway and the USA, specialized abortion clinics have been established. In the USA, larger clinics have a caseload of more than 10 000 abortions each year [12]. In France, New Zealand and the UK abortion is provided almost only in hospital. Abortion within dedicated clinics may be more economical and the service is provided by experts who may be more sensitive and sympathetic to women undergoing pregnancy termination. However, this approach separates abortion from other aspects of reproductive health care. In Scotland, where over 95% of abortions are performed in National Health Service hospitals, counselling for and performing abortions is part of the training of all gynaecologists unless they have moral or religious objections. Medical students and doctors planning to enter general practice are also exposed to all aspects of unwanted pregnancy [13]. In countries where abortion is largely confined to specialized clinics such as the USA, abortion is not always part of gynaecological training. Without exposure during their training to the relevant issues and to women who are seeking abortion, doctors may become increasingly reluctant to be involved with the provision of services.

While the manner in which abortion services are provided varies widely between countries it is possible to devise a set of guidelines for a high-quality service that is universally applicable to all providers. Such a template for abortion services should aim for a safe, efficient and comprehensive service that allows women to exercise choice over their treatment and which respects their dignity. This template can be divide into four elements:

1 pregnancy diagnosis and determination of gestational age;
2 information, medical assessment and counselling;
3 provision of the abortion;
4 post-abortion services.

### *Pregnancy diagnosis and determination of gestational age*

An abortion service should be able to offer immediate biochemical pregnancy testing, as waiting for results may cause delay and certainly increases anxiety. Ultrasound scanning facilities should be available to determine the gestational age and viability of the fetus when there is clinical doubt. A few women will not be pregnant or will have an ectopic or non-viable pregnancy. In such cases, referral for the management of abnormal pregnancy or investigation of amenorrhoea should be available and women should receive advice about contraception (and supplies) if appropriate. The ability to scan the patient is also useful in the assessment of incomplete or failed abortion at follow-up.



### *Information, medical assessment and counselling*

Counselling and written information about abortion, as described above, should be available to all women seeking abortion. It must be possible for women who are uncertain about their decision to see a counsellor on more than one occasion. In the UK, it is estimated that 90% of women who approach a doctor to discuss it will choose abortion, 8% will choose to continue with the pregnancy, 1% will present too late for legal abortion and 1% will not be pregnant. For those women who are too late and for some of those who choose to have the baby, information about social security benefits and adoption, and referral to social services where they exist, should be available.

Abortion services should have the ability to assess the general health of the woman and her suitability for the various methods of abortion. A check-list of indications and contraindications to the available techniques is useful in a clinic setting. Blood should be taken for ABO and rhesus (D) testing and for any other appropriate investigations such as sickle cell screening. Whether the service chooses to screen for genital tract infection, particularly *Chlamydia*, or simply to treat everyone with prophylactic antibiotics will depend on the background incidence of infection in the local population. Women considered to be at high risk of hepatitis B or human immunodeficiency virus (HIV) should be offered screening with appropriate counselling. Such tests should never be made a condition of having the abortion and women who refuse screening should be treated as high risk during the abortion procedure. Cervical screening should be offered in accordance with national screening policies.

### *Provision of the abortion*

In general, the earlier the abortion is done, the safer it is. Surgical abortion

is associated with a higher failure rate, however, if performed before 7 weeks of gestation. The abortion should be provided at the earliest possible gestation and preferably completed within 7 days of the initial request. It is well recognized that the mortality and morbidity associated with the procedure increase with the gestation of the pregnancy at the time of termination. The risk of major complications doubles when termination is carried out at 15 as compared with 8 weeks gestation [14]. International comparisons of gestational age at the time of abortion are difficult to obtain but there are wide variations in the proportion of abortions performed at different gestations in different countries. In former Czechoslovakia, late abortions involve a prolonged stay in hospital and a charge to the woman, early abortion is encouraged and some 85% are performed before 9 weeks. In some countries such as India, lack of medical resources mean that women have to wait for abortion until they are in the second trimester. The same is true in parts of England where National Health Service provision of abortion is insufficient for the demand among women who cannot afford private treatment.

Gestational age also determines the method of choice. Medical abortion is only available to women in the UK and Sweden up to 63 days of amenorrhoea and up to 49 days in France. Clearly, early treatment increases the opportunities for a choice of method in the first trimester. Long delays also increase the woman's anxiety over her unwanted pregnancy.

Abortion should be available to women of any gestation up to the legal limit for that country, and this means having a variety of methods available. Women who present early enough should have a choice between medical or surgical induction of abortion. Vacuum aspiration has been the method of choice for early surgical termination of pregnancy in industrialized countries for more than two decades. In his world review made in 1990, Henshaw [12] reports that over 95% of surgical abortions were performed by suction in most of northern Europe and the USA. Yet, dilatation and curettage (D & C) is still the standard method for uterine evacuation in many Eastern European countries—52% in Hungary [12]—and in developing countries [15] where most physicians are not trained in suction aspiration. D & C requires more cervical dilatation, carries more risk of uterine injury and a higher incidence of retained products of conception and, is thus associated with a significantly higher complication rate and adverse future reproductive outcome [16]. Vacuum aspiration is less painful than D & C and is thus associated with less need for analgesia.



Vacuum aspiration can be achieved by the use of either electric or manual pump, the latter (manual vacuum aspiration, MVA) involves the use of a hand-held syringe allowing its use in clinics without electricity. MVA is a simple procedure [15] appropriate for use by trained non-medical health workers. Its use in the management of abortion complications in countries such as Nigeria and Nicaragua where previously D & C under general anaesthesia was used, has had a significant effect on maternal mortality and morbidity from illegal abortion [17].

Vacuum aspiration can be performed under either local or general anaesthesia. In many countries, developed and developing, local anaesthesia is the method of choice, although in the UK the great majority of abortions are performed under general anaesthesia. General anaesthesia necessitates the use of an operating theatre, a trained anaesthetist and a longer recovery period and these requirements may add to the delay in treatment particularly in the developing world where the demands on operating theatre time can be immense. Some evidence suggests that the use of general anaesthesia increases the risk of the procedure. In the USA, the mortality rate is two to four times greater when general rather than local anaesthesia is used for first-trimester abortion [18]. In countries where both techniques are available with safety, the woman should have some involvement in the choice of anaesthetic.

Preoperative treatment with a cervical priming agent has been shown to reduce the risk of haemorrhage and genital tract trauma associated with vacuum aspiration. Prostaglandins, laminaria tents and the anti-progesterone RU 486 are all effective. Pretreatment of the cervix adds to the cost of the procedure and may be difficult to organize because of time constraints. Cervical trauma is more common in women under the age of 17 years and uterine perforation is associated with increasing parity and increasing gestation [19]. It would seem reasonable to select women for cervical priming on the basis of age, parity and gestation.

Medical termination of early first-trimester pregnancy using a combination of RU 486 and prostaglandin has been available in France since 1988, the UK since 1991 and Sweden since 1993. The incidence of serious complications is probably similar to that associated with surgical abortion, but because 95% of women need neither anaesthesia nor instrumentation of the uterus, large randomized trials may eventually show medical abortion to be safer. In France and the UK, around 20–25% prefer medical abortion [20] and, in countries where RU 486 is licensed, women who have no contraindications to either method should have a choice.

Second-trimester abortion is less common—it accounts for 10–15% of all legal abortions in the UK—but, is associated with a disproportionately high level of morbidity, with many of the complications relating to the specific method used to terminate the pregnancy. There are very few large randomized studies and it is difficult to determine whether there is a 'best method' for mid-trimester abortion. D & E is the most widely used method in many countries including the USA, Canada, Denmark, England and Wales, New Zealand, Norway and the former West Germany, and the method has proved to be consistently safer than instillation procedures (at least in the USA at gestations up to 16 weeks). The latter involve the instillation, either intra- or extra-amniotically, of prostaglandins, hypertonic saline, urea or ethacridine lactate. Skilled personnel are required to carry out these procedures and the abortion (the woman is conscious) tends to be painful and prolonged. With the exception of ethacridine lactate all the substances are potentially toxic (for review see [21]). The development of stable prostaglandin analogues has allowed the vaginal administration of prostaglandins, a route that is much safer than instillation. In 1990, Scotland and Finland were the only countries with a significant incidence of medically induced—rather than surgical—second-trimester abortions. In Scotland, the administration of prostaglandin vaginally is the method of choice, instillation being rarely used. The induction–abortion interval is significantly reduced by pre-treatment with RU 486 [22], and where the compound is available the combination of vaginal prostaglandins with antiprogesterone pretreatment may be recommended.

Abortion beyond 18 weeks gestation is rare and in many countries it is either illegal or only available for pregnancies complicated by severe fetal malformation. Particularly distressing for both the mother and the staff, these late abortions are often effectively managed with vaginal prostaglandins in combination with RU 486 with intra-amniotic urea or fetal intracardiac injection of potassium to minimize the chances of a live birth.

Whatever the method used, abortion should be available as a day-case or office procedure since this minimizes inconvenience to the woman concerned and reduces the cost. There is a worldwide trend towards shorter hospital stays in those countries where abortion is performed within a hospital setting. Overnight stay should be possible for women who have to travel long distances or who are unfit to go home after the procedure is completed.





### *Post-abortion services*

All women should receive contraceptive advice and, if appropriate, supplies before going home. They should also, as discussed above, receive written information about side effects, bleeding patterns and the resumption of fertility. All should be given a follow-up appointment within 3 weeks, either with the clinic that carried out the abortion or a suitable alternative doctor. At follow-up a pelvic examination should confirm complete abortion and the absence of infection. Discussion should include contraceptive advice and post-abortion counselling if required.

Abortion providers should participate in relevant health promotion programmes and should undertake regular audit of their service. They should be aware of and able to incorporate developments in technical and clinical practice. The service should be sensitive to the special needs of certain groups of patients including the very young, women from ethnic minorities and those with disabilities. In 1992–93 in the UK, the Birth Control Trust (BCT) circulated a model service specification for women requesting abortion [23]. Although written specifically for service provision in the UK, where abortion is provided free of charge on the National Health Service, the BCT's template for a service is a detailed and useful document for providers wishing to improve or audit their service.

## Conclusion

As we approach the next century, unsafe abortion is one of the major concerns facing people involved in reproductive health care. Worldwide it results in about 70 000 maternal deaths each year [11] and, yet, if provided under modern medical conditions in developed countries it is safer than pregnancy and childbirth. In their paper on the role of health care systems in abortion provision, McLaurin *et al.* [17] argue that providers 'need to examine existing services in light of women's needs, discover the barriers that hinder women's access to abortion care, and implement mechanisms to ensure that appropriate care is both available and accessible'.

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# The Acceptability of Medical Abortion and Other Uses of Mifepristone

*Anna Glasier*

*For the great majority of women the decision to have a pregnancy terminated is a difficult and painful one. The circumstances surrounding the need for abortion, such as the end of a relationship, are often distressing. Many women feel guilty about destroying the fetus and most are fearful about the abortion procedure. Since the development of a medical method for inducing abortion – mifepristone (first known as RU486) plus prostaglandin – in countries where the two drugs are licensed and in settings where medical techniques are available, women are being given a choice as to how they would prefer their pregnancy to be terminated. The freedom to choose the method of abortion may help to alleviate some of their anxiety and it is interesting to review why women choose one method rather than another. This paper reviews existing studies and discusses the potential limitations on the development of mifepristone for contraceptive use, for emergency contraception and other possible indications because of anti-abortion pressure.*

THE acceptability of medical abortion using mifepristone has been assessed in a number of cultural settings – Scotland,[1,2,3] England,[4] Sweden,[5] France,[6] Denmark,[7] Hong Kong,[8,9] and the USA.[10] The studies differ quite significantly, however, and are difficult to compare. Most were undertaken when RU486 was new and at a time when RU486 was unlicensed in the particular country where the study was done.

Many women are understandably hesitant to opt for a new and relatively untested treatment in whatever field of medicine, and this almost certainly affects not only which method they choose but also colours their experience of it. Many of the studies were undertaken as part of a trial of the efficacy of the method. In the Oxford study,[4] for example, women were invited either to participate in the study or to undergo routine surgical abortion. They were not simply choosing between two methods, but also whether to participate in a trial or not.

Where an acceptability study is tacked on to an efficacy study, the demands of the study itself undoubtedly influence the woman's choice of method too. In Tang's pilot study,[8] for example, women choosing medical abortion had to attend the study site on seven separate occasions while those choosing surgical abortion had to attend only twice.

Comparability of the studies is also complicated by significant differences in the details of the abortion method. Surgical abortion may be done under local or general anaesthetic, while medical abortion may involve the use of prostaglandins administered vaginally rather than intramuscularly. One of the studies[7] used mifepristone alone.

The duration of hospital stay also varied considerably. In one Scottish study,[2] the women were asked to stay in hospital for only four hours on the day of prostaglandin administration, compared with six hours in Hong Kong.[8] Again, in the Hong Kong centre[8] surgical abortion involved an overnight stay in hospital which was not required in Scotland.[3]

Despite these major differences there are nevertheless enough similarities to allow some general comments about the acceptability of medical abortion with RU486. Most studies determined the reasons why women chose either medical or surgical abortion, whether women who chose one or other method had certain characteristics in common, and tried to make some standard assessment of acceptability by asking which method a woman would recommend to a friend or opt for in the future should the need arise.

Perhaps the commonest reason why women

have chosen medical abortion as opposed to vacuum aspiration is the perception that the former is a more 'natural' procedure, which avoids exposure to general anaesthesia. In Hong Kong[8] some women felt less guilty about having an abortion because the medical method seemed more like a natural miscarriage. The fear of general anaesthesia is obviously not an issue if surgical abortion is performed under local anaesthesia. In the French study[6] only nine per cent of women chose vacuum aspiration under general anaesthesia while 27 per cent chose vacuum aspiration under local anaesthesia. Even when local anaesthesia was available, however, the great majority of women (62 per cent) opted for medical abortion.

A minority of women, on the other hand, chose surgical abortion in the Hong Kong study[8] because they wanted to be unconscious and unaware of events. For some women the anxiety associated with 'seeing the baby' prompted a choice of general anaesthesia. In fact, this is not the case during first trimester medical abortion, when only blood and tissue are visible, so this fear is unfounded, a point which can be made during counselling.

In most studies, some women's choice of method has depended on their perception of its safety. Perceptions have varied considerably, with some women concerned about the safety of the drugs used for medical abortion and others concerned about the use of instruments for surgical abortion. As medical abortion becomes more widespread, the fear of the drugs will most likely decrease for many women.

Medical abortion currently requires more visits to the hospital or clinic and a 48-hour wait between the two parts of the procedure. Many women have chosen surgical abortion because it appears to be quicker and to demand less time off work, unless an overnight stay is required, which is still the case in some countries. Moreover, the 48-hour wait inherent in medical abortion is a time of anxiety which some women feel unable to cope with.

For some women the fear of side effects has deterred them from choosing medical abortion. In the multicentre study undertaken in the United Kingdom,[11] 21 per cent of women complained of severe pain in the two days following prostaglandin administration and around 30 per cent of all participants required non-narcotic analgesia. In addition, between 13 and 37 per cent needed narcotic analgesia, but this depended both on parity and also highly significantly on the centre where the abortion took place. Twenty-five per cent of the women vomited and 13 per cent experienced diarrhoea after prostaglandins were given.

Thong and colleagues[2] working in Edinburgh found that the need for analgesia was related to length of gestation, parity and a history of dysmenorrhoea – all factors which can be determined during the time of counselling a woman about her choice of method.

Medical abortion is thought to involve more blood loss post-operatively and a longer duration of bleeding than with surgical abortion. In fact, the total blood loss is not greater. However, with a surgical procedure much of the bleeding occurs acutely at the time of operation and is unnoticed by the woman.

In most studies, medical abortion seemed more likely to be chosen by women who were younger, single, better educated and of a higher socio-economic status. In an as yet unpublished audit from Edinburgh[12] women who smoked were more likely to choose surgical abortion.

In all the published studies, the vast majority of women were happy with whichever method they had chosen, said they would choose the same procedure again if the need for abortion arose, and would recommend it to a friend. It is difficult for a woman to choose between two methods unless she has experienced both and is faced with a choice on a third occasion. Even then, the circumstances surrounding the unplanned pregnancy and the professional staff involved with counselling and carrying out the abortion will almost certainly be different, and both will have a major influence on a woman's feelings about the procedure.

Perhaps the most helpful study of acceptability comes from Aberdeen[3] in which the 54 per cent of women who felt unable to choose between the two procedures were randomised. As with other studies, around 90 per cent of the women who made a choice were happy with the outcome, but there were significant differences in the extent of dissatisfaction among those who were randomised. Only two per cent of randomised women were unhappy with surgical abortion, but 22 per cent were unhappy with the medical method. In contrast, in another study

from Aberdeen,[1] ten out of 13 women who had experienced both surgical and medical abortion said that they preferred medical abortion. This study is the only one which reported psychiatric morbidity associated with abortion, but it found no difference between medical and surgical methods.

Given the choice between surgical and medical methods of inducing abortion, many women seem to prefer the medical approach. Whatever method they choose, a small minority of women find the experience unsatisfactory and it is possible that this is more likely when medical abortion is chosen. When any new therapy is introduced – particularly with the amount of publicity that surrounded RU486 abortion – expectations may be unrealistically high. The provision of accurate and detailed information about all abortion procedures should overcome this problem. Indeed, the very fact that women themselves have a say in how the abortion is performed probably increases the acceptability of the method they choose.

## Other uses of Mifepristone

RU486 has great potential for use as a contraceptive method and a number of approaches – very low dose daily administration, once-a-week pills, once-a-month pills, and emergency post-coital contraception – are all being investigated. To date, researchers have concentrated on the efficacy of these methods rather than acceptability.

Protocols for the development of new contraceptive techniques are complicated and entail a multitude of frequent and often invasive investigations, such as blood tests, cervical smears and endometrial biopsies, which are not necessary when the method becomes available for routine use. Moreover, phase 1 studies are often undertaken on women who are not at risk of pregnancy, women who are sterilised or using a barrier method of contraception, so true acceptability is almost impossible to measure.

We undertook a survey[13] of women in Scotland, Slovenia and Romania to determine the theoretical acceptability of a once-a-month pill. The once-a-month concept was acceptable, but in Scotland, and to a lesser extent in Slovenia, the acceptability depended on the mode of action. Only 24 per cent of the women in Edinburgh were prepared to use a pill which acted after implantation had occurred and only 33 per cent in Slovenia.

In two studies of 600 mg RU486 as an emergency post-coital contraceptive[14,15] the incidence of side effects was highly significantly less in women who took RU486 in comparison with those given the standard combined oestrogen-progestogen (Yuzpe) regimen. Moreover, the Yuzpe regimen requires the ingestion of two doses of pills separated by 12 hours, while RU486 needs to be taken only once. Although this was not specifically measured, it is likely that the single dose and reduced side effects with RU486 given in this manner would make it more acceptable than the Yuzpe regimen.

RU486 has great potential for development as a contraceptive and indeed, for other uses such as the treatment of breast cancer. Yet the use of RU486 and any other anti-progestin that may be developed will be limited if it is only thought of as an 'abortion pill'. Thus, the introduction of an anti-progestin, for whatever other therapeutic use, into a country where abortion is illegal or where RU486 has not been licensed as an abortifacient may be extremely difficult. Even in countries where RU486 is licensed for the induction of early abortion, it is currently subject to more controls than perhaps any other drug. In the United Kingdom, for example, both the drug licensing authority and the manufacturers are responsible for a set of stringent restrictions on its provision.

In some countries, such as the USA, drug regulatory authorities have a legal mandate to consider a product application only for the therapeutic purposes for which approval is sought. Nevertheless, ideological pressure, which may even come from the government itself, may be hard to resist. A review of the science and politics of RU486 in 1989 in the USA says:

*'...As long as the deadlock on RU486 continues, its other potential lifesaving applications will remain unexplored.'*[16]

This review points out the fear that the licensing of the drug for one purpose would inevitably lead to it ultimately being used for abortion as well. This would almost certainly be the case in other countries. In the United

Kingdom, once a drug becomes available a doctor is free to use it as he or she sees fit. If the use accords with accepted clinical practice, legal redress is unlikely. Thus, many doctors prescribe oral contraceptive pills containing 50 mcg oestrogen for emergency contraception, even though the pills are not licensed for this purpose. Because the practice is so widespread and clinically sound, it is acceptable medico-legally. In this way, if RU486 were licensed for the treatment of breast cancer in a country where it was not licensed for abortion, a doctor could successfully argue for the validity of its use as an abortifacient, demonstrated in evidence from other countries.

Even if doctors themselves refrained from providing RU486 for the unlicensed purpose of abortion, once it was available for other purposes and if it were available over the counter, there would be potential for its use directly by women as an abortifacient, as has happened with the anti-ulcer drug misoprostol (a prostaglandin) in Brazil and elsewhere, for inducing abortion illegally.[17]

If contraceptives containing an anti-progestin could only be administered in a controlled manner, in the way that mifepristone is administered today for early abortion, then it would not be possible to develop anti-progestins for contraception. Hence, either we have to accept that anti-abortion pressure may prevent the development or licensing of a range of therapeutic uses for mifepristone, even where it would be the preferred treatment, as seems to be the case with its use for emergency contraception, or we have to find a way to overcome the reluctance to license mifepristone for all of the scientifically proven indications it may have, starting with early abortion.

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## RÉSUMÉ

La mise au point d'une méthode médicale pour déclencher l'avortement – l'association de mifépristone (ou RU486) et de prostaglandine – permet désormais aux femmes de choisir la façon dont elles préfèrent mettre fin à leur grossesse, dans les pays où les deux produits sont autorisés, et où on peut avoir accès à des techniques médicales. La liberté de choisir la méthode d'interruption de grossesse peut alléger quelque peu l'angoisse des avortées. L'article fait une revue des études actuelles et se demande pourquoi des femmes choisissent une méthode plutôt qu'une autre. Il discute les potentialités de la mifépristone à des fins contraceptives, pour la contraception d'urgence et dans d'autres indications éventuelles. La pression des adversaires de l'avortement peut empêcher de développer ou de faire homologuer diverses utilisations thérapeutiques de la mifépristone, même là où ce produit semble devoir être le traitement de choix, par exemple pour la contraception d'urgence. Il faut ou bien l'accepter, ou trouver des moyens de vaincre les répugnances à son homologation pour toutes les indications avérées qu'il peut avoir, à commencer par l'avortement précoce.

## RESUMEN

Desde la invención de un método médico para inducir el aborto (el mifepristone, conocido inicialmente como RU486, más la prostaglandina) la mujer tiene la posibilidad de elegir cómo prefiere interrumpir su embarazo en aquellos países en que ambas sustancias están autorizadas, y en contextos en los que existe acceso a técnicas médicas. La libertad de poder elegir el método de aborto puede contribuir a aliviar en parte su ansiedad. Este ensayo hace una revisión de los estudios existentes y examina por qué las mujeres escogen uno u otro método. Discute también el potencial del mifepristone para uso anticonceptivo, como anticonceptivo de emergencia y otras posibles indicaciones. La presión en contra del aborto puede impedir el desarrollo o autorización de toda una variedad de usos terapéuticos del mifepristone, incluso en casos en los que sería el tratamiento preferido, como parece suceder en el caso de su utilización como método anticonceptivo de emergencia. O bien aceptamos esto o debemos encontrar la forma de superar la reticencia a autorizar esta sustancia para todas la indicaciones demostradas que pueda tener, comenzando por el aborto temprano.

Review Article

*Drug Therapy*

ALASTAIR J.J. WOOD, M.D., *Editor*

# EMERGENCY POSTCOITAL CONTRACEPTION

ANNA GLASIER, M.D.

EMERGENCY postcoital contraception may be defined as the use of a drug or device to prevent pregnancy after intercourse. Unwanted pregnancy is common; worldwide, about 50 million pregnancies are terminated each year.[1] It has been calculated that each year the widespread use of emergency contraception in the United States could prevent over 1 million abortions and 2 million unintended pregnancies that end in childbirth.[2]

A variety of different methods of emergency contraception are available (Table 1). The first to be described was high-dose estrogen, although currently the most widely used is a combination of estrogen and progestin. Recent interest in the development of alternative regimens has led to trials of progestin alone, the antigonadotropin danazol, and the antiprogestogen mifepristone (RU 486) for postcoital contraception. Highly effective, but much less convenient, is the postcoital insertion of an intrauterine contraceptive device.

## PROBABILITY OF CONCEPTION

The probability of conception after a single act of intercourse has been calculated to be about 33 percent per cycle if intercourse occurs on average every other day[1,2]; if it occurs only once per week, the risk of pregnancy is only 15 percent. Most women who have unprotected intercourse on a single occasion therefore will not conceive. Conception occurs only around the time of ovulation. Surprisingly, the number of days of the menstrual cycle during which a woman is fertile (i.e., on which conception could result if intercourse occurred) has been difficult to quantify. Although sperm remain in the female genital tract and are capable of fertilization for up to five days after ejaculation, the egg appears to be capable of being fertilized for only about 24 hours.

In a recent study of couples actively trying to conceive, in which hormone measurements were used to determine the timing of ovulation, the fertile period lasted about six days, ending on the day of ovulation.[1,2] There were no conceptions when intercourse occurred after the day of ovulation; acknowledging the small sample size in their study, however, the authors concluded that a probability of conception of up to 12 percent was theoretically possible if intercourse occurred on the day after ovulation. In that study, in which pregnancy was detected on the basis of urinary measurements of human chorionic gonadotropin, 24 percent of the pregnancies ended within six weeks after the last menstrual period and only 68 percent resulted in childbirth.

## MODE OF ACTION OF EMERGENCY CONTRACEPTION

Emergency contraception could work by inhibiting or disrupting ovulation, interfering with fertilization or the transport of the embryo to the uterus, or inhibiting its implantation in the endometrium. Any device or drug that acts after implantation is conventionally regarded as an abortifacient rather than a contraceptive. In theory, the most effective method of emergency contraception would be one that inhibited implantation, because it would prevent conception at whatever time in the cycle intercourse occurred, even after ovulation. A method that affected ovulation or fertilization would prevent most but not all pregnancies, because women who used the method after they had already ovulated might still conceive. In practice, the precise mode of action of currently available emergency contraceptives is not known, although there is evidence of effects at several critical stages of the reproductive cycle.

### Effects on Ovulation

Most of the research on estrogen alone has concentrated on its effects after ovulation. In theory, large doses of estrogen given before ovulation might be expected to inhibit follicular development and maturation or the release of the ovum itself; there is, however, no evidence of any of these actions. Given before or at the time of ovulation, both estrogen plus progestin and danazol sometimes inhibit or delay ovulation.[3-5] Mifepristone inhibits ovulation,

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TABLE 1. METHODS OF EMERGENCY CONTRACEPTION.

| REGIMEN | TIME AFTER INTERCOURSE* | STATUS OF METHOD | REPORTED EFFICACY† | SOURCE OF DATA |
|---|---|---|---|---|
| Estrogen and progestin (100 μg of ethinyl estradiol and 0.5 mg of levonorgestrel given twice, with 12 hr between doses) | 72 hr | Licensed in some countries since early 1980 (e.g., United Kingdom, the Netherlands); available unlicensed in the appropriate combination of oral-contraceptive pills | 75–80% of pregnancies prevented | Meta-analysis of 10 trials involving >5000 women[3] |
| Levonorgestrel (0.75 mg given twice, with 12 hr between doses) | 48 hr (possibly up to 72 hr) | Licensed in some countries in Eastern Europe and Asia | Equivalent to estrogen–progestin | One randomized trial involving 350 women[4] |
| High-dose estrogen (e.g., 5 mg of ethinyl estradiol daily for 5 days) | 72 hr | Licensed in the Netherlands; little used elsewhere | Equivalent to estrogen–progestin[5] | Randomized trial involving 250 women; early trials suggested failure rates <1%[6,7] |
| Mifepristone (a single 600-mg dose) | 72 hr | Widely used in China in a variety of lower doses; not licensed anywhere else for emergency contraception | 100% effective | Two randomized trials involving a total of 600 women[8,9] |
| Danazol (400 to 800 mg given twice 12 hr apart or 400 mg given 3 times at invervals of 12 hr) | 72 hr | Used only under research conditions | Reports vary from failure rates of <1%[10] to ineffective[9] | Two randomized trials, one involving >1700 women and suggesting failure rates of about 1%,[10] and the other involving 193 women and suggesting little or no effect[9] |
| Copper intrauterine device | Up to 5 days after the earliest estimated day of ovulation | Available worldwide, but not licensed for emergency contraception | Failure rates <1% | Meta-analysis of 20 published studies involving >8000 women[11] |

*The times given are for the first dose.

†Data on efficacy are not comparable since not all are based on exposure during the fertile phase of the cycle (see the text).

even when given at low doses during the follicular phase,[16] and the administration of mifepristone as a postcoital contraceptive before ovulation significantly delays the onset of menses, indicating the inhibition of ovulation.[8]

#### Effects on Fertilization

There is no direct evidence that any of the hormonal methods of emergency contraception prevent fertilization, although such an effect cannot be ruled out. The intrauterine contraceptive device can compromise fertilization by its toxic effects on sperm[17]; if it is inserted after intercourse but before ovulation, it could theoretically work by preventing fertilization.

#### Effects on Gamete Transport

Although high-dose estrogen impairs the transport of the ovum in some animal species,[18] there is no evidence of such an effect in humans. Early trials of high-dose estrogen given after intercourse to women at risk for conception were associated with an increased incidence of ectopic pregnancy,[19] but it is likely that, as with the intrauterine contraceptive device, this method is better at preventing intrauterine pregnancies than tubal pregnancies.

#### Effects on the Function of the Corpus Luteum

Abnormalities of luteal-phase progesterone secretion are associated with a reduction in fertility. Since the corpus luteum is derived from the ovarian follicle, events that affect the developing follicle may influence the function of the corpus luteum. Although estrogen plus progestin (given either before or after ovulation),[13-15] danazol,[14,15] and high-dose estrogen[20] all reduce the magnitude of the midcycle surge in serum luteinizing hormone, reduce progesterone concentrations in the luteal phase, or both, it is not known whether such changes are incompatible with pregnancy. There is better evidence of an effect of mifepristone on the corpus luteum; when given in the mid-luteal or late luteal phase of the cycle, it induces regression of the corpus luteum in about 50 percent of women.[21]

#### Effects on Implantation

Mifepristone administered immediately after ovulation delays endometrial maturation without affecting ovarian hormone production or menstrual bleeding,[22] and when given in this way it prevents pregnancy.[23] Insertion of an intrauterine device after ovulation causes histologic changes in the endometri-

um that would be expected to impair implantation.[24] In contrast, although the postovulatory administration of estrogen[25] or levonorgestrel[26] inhibits implantation in some animals, evidence of similar effects in women has been difficult to obtain. Minor changes in the histologic and biochemical features of the endometrium occur when high-dose estrogen,[6] the estrogen–progestin combination, or danazol is administered after ovulation,[27] but the effects may not be sufficient to inhibit implantation. In a recent morphometric study, postovulatory administration of estrogen plus progestin had only minor effects on the endometrium, and danazol had no effect.[15]

#### Interruption of Pregnancy

It is unlikely that danazol, estrogen, or progestin, either alone or in combination, interrupts early pregnancy in women once implantation has occurred. In contrast, mifepristone is effective after implantation in 80 percent of women.[28] Since implantation occurs about seven days after ovulation, emergency contraception within five days after intercourse cannot be considered to interrupt pregnancy.

Conception is much less likely if intercourse occurs after ovulation. At least one trial suggested that both estrogen plus progestin and danazol are less likely to be effective as postcoital contraceptives if they are taken after ovulation.[9] The balance of evidence suggests that the most widely used hormonal emergency contraceptive, estrogen plus progestin, works mainly by inhibiting or delaying ovulation. If the intrauterine contraceptive device is inserted or mifepristone is given after intercourse, the mode of action will depend on the timing of treatment in relation to ovulation.

## INDICATIONS FOR EMERGENCY CONTRACEPTION

Emergency contraception is useful after unprotected intercourse or withdrawal that occurs too late and for couples who recognize the failure of a barrier method, such as a burst condom. In a recent study of condom breakage and slippage, 4 to 7 percent of couples using this form of contraception in the United States had a recognized condom failure during a period of up to three months.[29] Emergency contraception is not usually indicated when one or more oral contraceptive pills have been forgotten, because there are established and effective rules for the use of a barrier method as secondary prevention under these circumstances (Fig. 1).

## EFFICACY OF EMERGENCY CONTRACEPTION

The efficacy of emergency contraception is difficult to quantify. Most studies include large numbers of young women of unproved fertility, and for obvious reasons there can be no control group. Some couples are not certain that there was spillage of seminal fluid when a condom burst or that ejaculation actually occurred. Many authors simply report failure rates in terms of the number of pregnancies among the women treated, but most of these women would not have conceived even if they had not used emergency contraception. More recently, attempts have been made to estimate the number of women genuinely at risk of pregnancy — that is, those who had unprotected intercourse during the fertile period — and to relate the number of actual pregnancies to the number of expected pregnancies. Even this method has its shortcomings, because neither the precise timing of intercourse nor the exact date of the last menstrual period is always accurately recalled, and for individual women the day of ovulation may vary by as much as two or three days in each cycle. Thus, the timing of exposure to the risk of pregnancy in relation to the day of ovulation is, even in these well-documented studies, an educated guess. In a recent meta-analysis of 10 published studies in which data on the menstrual cycle and the timing of intercourse were reported, the efficacy of estrogen plus progestin was estimated to be 74 percent, on average.[3] Although mathematical calculations have their appeal, when faced with the possibility of an unwanted pregnancy, many women would use a method that was only 50 percent effective or even less if there was no alternative.

## COMBINED ESTROGEN AND PROGESTIN

The estrogen–progestin regimen is two doses of a combination of 100 $\mu$g of ethinyl estradiol and 0.5 mg of levonorgestrel each, the first dose taken within 72 hours after intercourse and the second 12 hours later. A licensed product is available in several countries in Western Europe and in New Zealand (marketed under a variety of trade names, such as Schering PC4 in the United Kingdom and Tetragynon in Switzerland). First described in 1977 by Yuzpe and Lancee,[30] the combination therapy is often referred to as the Yuzpe regimen. The same hormones are available in some brands of combined oral contraceptive pills, and these are often used in countries where a marketed preparation is unavailable. It is not known whether the estrogen–progestin regimen is effective if taken later than 72 hours after intercourse,[31] nor whether combined oral contraceptives containing other progestins administered in a similar manner are effective. Neither is it known whether the two-dose regimen is strictly necessary.

Nausea (in up to 50 percent of women) and vomiting (in up to 20 percent) are the main side effects of this regimen.[8] Both, in theory, may occasionally interfere with the woman's taking the second dose, and vomiting may reduce efficacy if it occurs within two hours after the medication is taken, in which

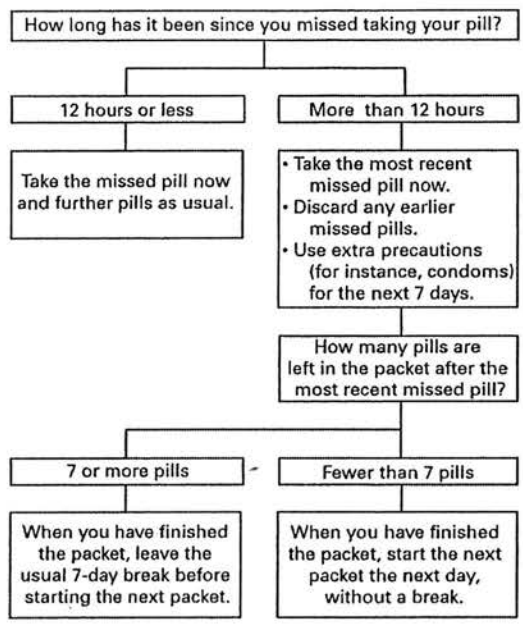


**Figure 1.** Scheme for the Prevention of Pregnancy in Women Who Miss One or More Oral-Contraceptive Pills.

case absorption may be reduced. Some clinics routinely provide an antiemetic drug, but there are no data to support this practice. Moreover, in practice, nausea and vomiting seldom prevent women either from taking the second dose or from using the regimen on another occasion; vomiting within two hours after swallowing the tablets is uncommon; and failures of emergency contraception do not appear to be associated with vomiting. Subsequent menses normally occur at the expected time[8] but may be heavier than usual, and some women have mastalgia for a few days after treatment.[30]

Although it is widely used in Europe, there are very few data on the safety of the estrogen–progestin regimen. Long-term use of the combined oral-contraceptive pill is associated with an increased risk of both arterial disease (myocardial infarction and cerebrovascular accident)[32] and venous disease (deep venous thrombosis and pulmonary embolism).[33] The risk of venous thromboembolism is thought to be dose-dependent, and it is higher with pills containing 50 $\mu$g of ethinyl estradiol than with low-dose pills (containing 30 to 35 $\mu$g).[34] Because the estrogen–progestin regimen exposes women to the same type of hormones, there has been a tendency to extrapolate from the risks of combined oral contraceptives. Although the estrogen–progestin regimen exposes a woman to a total of 200 $\mu$g of ethinyl estradiol, the exposure is short-term. One small study of the high-dose estrogen regimen[35] demonstrated a detrimental effect on clotting factors, but a similar study failed to show any consistent effect of estrogen plus progestin.[36]

Few adverse events associated with estrogen plus progestin have been reported in the United Kingdom (Committee on Safety of Medicines: personal communication). In the 13 years since Schering PC4 was licensed, it has been used on more than 4 million occasions. By the middle of 1996, there had been 115 reports of 159 "reactions" (some women had more than 1), 61 of which were pregnancies. In the United Kingdom only three cases of venous thrombosis (one fatal) and three cases of cerebrovascular disorder have been reported, and in none was the relation between the administration of estrogen and progestin and the event clear-cut. In contrast, the risk of venous thrombosis during pregnancy is on the order of 60 per 100,000 per year. Both the World Health Organization,[37] which in 1996 added the estrogen–progestin regimen to its "essential drugs list," and the International Planned Parenthood Federation[38] have stated that there are no absolute contraindications to the use of the estrogen–progestin regimen except known pregnancy.

Reliable data on the outcome of pregnancies that occurred after estrogen and progestin were taken are lacking, but the absence of demonstrable teratogenicity of combined oral contraceptives[39,40] and the timing of emergency contraception — long before organogenesis starts — are reassuring. Thus, the estrogen–progestin regimen is contraindicated in pregnancy only because it does not work once pregnancy is established, not because it is known to be harmful.

## ESTROGEN ALONE

High doses of estrogen — usually ethinyl estradiol in a variety of regimens — given for five consecutive days are extremely effective as postcoital contraception, with failure rates of only 0.1 to 1 percent.[6,7] Side effects, particularly nausea (in 70 percent of women) and vomiting (in 33 percent), are common, and many clinicians stopped using estrogen alone when the estrogen–progestin regimen was described. The so-called five-by-five regimen (five tablets of 1 mg of ethinyl estradiol each, given daily for five days) is still used in the Netherlands,[41] where some clinicians believe it is more effective than the estrogen–progestin regimen. However, a double-blind, randomized study comparing the two regimens in the Netherlands demonstrated no difference in efficacy or, in fact, in the incidence of nausea and vomiting.[5]

## THE INTRAUTERINE CONTRACEPTIVE DEVICE

The copper-bearing intrauterine device is a highly effective postcoital contraceptive, with failure rates of less than 1 percent.[11,42] In the United Kingdom it is used for up to five days after the earliest estimated day of ovulation, which may, of course, be more than five days after intercourse. It is particularly appropriate for women who wish to use the intrauterine device as a long-term method of contraception. However, most women requesting emergency contraception are young and nulliparous, and it can be difficult to insert a device if the uterus is small. Because of the risk of inducing pelvic infection if the device is inserted in the presence of a sexually transmitted disease, it is commonplace to screen women for infection, or to give an antibiotic, before insertion.

## PROGESTIN ALONE

Progestin without estrogen has been tested as a postcoital agent in only one randomized trial.[4] Taken within 48 hours after unprotected intercourse, two 0.75-mg doses of levonorgestrel, given 12 hours apart, resulted in failure rates similar to those with the estrogen–progestin regimen (2.6 percent for estrogen–progestin vs. 2.4 percent for levonorgestrel). Side effects, however, were significantly less common with levonorgestrel. A levonorgestrel-only product (Postinor) is available from pharmacists in parts of Eastern Europe, the Far East, and many developing countries.

## DANAZOL

The antigonadotropin danazol is an effective emergency contraceptive when given within 72 hours after intercourse. In one study the failure rates were 1.7 percent among women given two doses of 400 mg each 12 hours apart and 0.8 percent among women given three doses at 12-hour intervals.[10] However, a randomized study in the United Kingdom comparing estrogen plus progestin with danazol (two doses of 600 mg each, given 12 hours apart) suggested that danazol may be ineffective when used after intercourse.[9]

## ANTIPROGESTINS

The antiprogestin mifepristone has also been tested as an emergency contraceptive. Two randomized trials,[8,9] involving a total of almost 600 women, compared 600 mg of mifepristone with the estrogen–progestin regimen. Mifepristone given within 72 hours after intercourse was 100 percent effective in preventing pregnancy, whereas the estrogen–progestin regimen was estimated to have prevented between 66 percent[22] and 83 percent[8] of pregnancies. The difference between the two regimens is not surprising, because mifepristone is known to inhibit implantation as well as ovulation and so, in theory, should almost always prevent pregnancy. All side effects were much less common among the women given mifepristone; however, in one of the studies 42 percent of women had a delay of more than three days in the onset of the next menstrual period.[8] This delay was particularly likely to occur if mifepristone was given during the follicular phase of the cycle, when it is known to inhibit ovulation.[16] This is an obvious drawback of mifepristone, because the onset of menses reassures the woman who has used emergency contraception that she is not pregnant. A lower dose of a mifepristone compound with a shorter half-life may not disrupt the timing of subsequent menses. Mifepristone is now used in a variety of doses in parts of China as the postcoital contraceptive of first choice.

## AVAILABILITY OF EMERGENCY CONTRACEPTION

Emergency contraception is not universally available. It is not licensed, for example, in France or in the United States, although in February 1997 the U.S. Food and Drug Administration (FDA) published a formal notice in the *Federal Register* stating that six brands of commonly used combined oral-contraceptive pills were safe and effective for emergency postcoital use.[43] The main reasons for the lack of wider use of emergency contraception were discussed at a meeting held in Italy in 1995.[44] The par-

ticipants concluded that both women and providers are, by and large, poorly informed about the available methods. Because currently available hormonal regimens must be started within 72 hours after intercourse, a woman has to know about the method before the need for it arises. A number of surveys in some developed countries have demonstrated that whereas knowledge of the existence of emergency contraception is widespread among selected populations of potential users[45,46] (including teenagers[47]), knowledge of the details and practicalities, particularly the time limit, is usually poor. In the United States, a toll-free emergency-contraception hot line operated by the Reproductive Health Technologies Project and Bridging the Gap Foundation (1-800-584-9911) provides callers with information about all available methods and about local providers. In the first year it was available, the service received more than 40,000 calls.

Very few products are marketed for emergency contraception, and pharmaceutical companies appear to be reluctant to enter the market. According to the FDA, no U.S. drug manufacturer has sought formal approval for the emergency use of an oral-contraceptive regimen, despite requests from the agency that they do so.[48] In 1996 several international agencies formed a Consortium for Emergency Contraception that was committed to making emergency contraception a standard part of reproductive health care throughout the world. Working in partnership with the pharmaceutical industry, the consortium aims to improve access through "model introductions" in selected countries of specially packaged and labeled products, including the little-researched progestin-only regimen.

In addition, providers in many countries seem reluctant to provide emergency contraception because it is confused with abortion. It cannot be stressed too strongly that if hormonal emergency contraception works largely by interfering with ovulation, then it cannot be regarded as an abortifacient. When administered within 72 hours after a single act of intercourse, even compounds known to interrupt established pregnancy cannot dislodge an implanted embryo, because implantation would not have occurred yet. For most providers and many potential users, acceptance of emergency contraception would improve if their knowledge improved and if the distinction between a method that a woman can use when she thinks that she might become pregnant (contraception) and something to use when she thinks she might already be pregnant (an abortifacient) were clearly understood.

Even in countries where hormonal emergency contraception is licensed and free, such as the United Kingdom, its use is limited by difficulty of access.[45] In the United Kingdom, emergency contraception must be prescribed by a doctor. Unprotected intercourse, particularly among young people, tends to occur on weekends, when clinics are closed and when calling the emergency doctor seems inappropriate. The proposal that Schering PC4 should be sold over the counter in pharmacies has been widely discussed in the United Kingdom.[49] Despite support for the proposal from the Royal College of Obstetricians and Gynaecologists, the Royal College of General Practitioners, and the Royal Pharmaceutical Society, it has not happened yet. The Ministry of Health in New Zealand had expected emergency contraception to be available over the counter by July 1996.[50] The New Zealand Medical Association and the Royal New Zealand College of General Practitioners opposed the move, however, as did the pharmaceutical industry, which is apparently concerned about misuse, incorrect use, and medicolegal risks. The Ministry of Health promised to allow pharmacists to cut up packets of pills and label them appropriately if the pharmaceutical industry did not respond to the request to change the prescription-only status of the marketed estrogen–progestin regimen. Despite even this governmental pressure, emergency contraception is not yet available over the counter in New Zealand. Of course, in countries where oral-contraceptive pills are available over the counter, hormonal regimens for emergency contraception are already available without prescription.

## CONCLUSIONS

Emergency contraception prevents unwanted pregnancy. The most widely used method, a combination of ethinyl estradiol and levonorgestrel, although it is marketed as an emergency contraceptive in only a few countries, is available throughout the world in the form of combined oral-contraceptive pills. Indeed, countless women already have supplies in their bathroom cupboards. When started within 72 hours after intercourse, the estrogen–progestin regimen has been estimated to be at least 75 percent effective and is safe. The antiprogestin mifepristone is even more effective and has fewer side effects.

Use of emergency contraception is limited largely by ignorance. Although it seems likely that the estrogen–progestin regimen works mainly by interfering with ovulation, it is nevertheless regarded by many as an abortifacient because it is taken after, rather than before, intercourse. This confusion is compounded when mifepristone is advocated for emergency contraception since, when taken after pregnancy is established, it can be and is used for the induction of abortion. The prevention of pregnancy before implantation is contraception and not abortion. Intervention within 72 hours after intercourse cannot possibly amount to abortion, because implantation is not achieved until at least seven days after ovulation and the egg is capable of being fertilized for only about 24 hours.

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# Emergency contraception

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Knowledge and use of emergency contraception world-wide is extremely limited. Recent research has demonstrated that levonorgestrel alone is at least as effective as the Yuzpe regimen and is much better tolerated. Levonorgestrel is likely to become the method of choice in the early 21st century. Mifepristone is highly effective even at doses which are not abortifacient. Efficacy cannot be calculated precisely, but all presently available methods seem to prevent at least 74% of unwanted pregnancies. The Yuzpe regimen inhibits or delays ovulation, but there is no good evidence that it prevents implantation. There are no data on the mechanism of action of levonorgestrel alone and the mode of action of mifepristone depends on when in the reproductive cycle it is used. Accessibility to emergency contraception is limited by the requirement for it to be prescribed by a doctor. Advanced provision of emergency contraception may prevent a significant number of unwanted pregnancies.

In the last decade of the 20th century, emergency contraception emerged from being the 'best-kept secret' in contraception to become one of the hottest topics in reproductive health.

Emergency contraception (EC) is defined as any drug or device which when it is used after intercourse, will prevent pregnancy. First described in the 1970s, the spread of emergency contraception has been slow and patchy. A licensed product became available in the UK in 1984. It took an invitation from the Food and Drug Administration (FDA) to manufacturers before a dedicated product became available in the US in 1998 and France got its first emergency contraceptive in 1999.

Research in the 1990s concentrated on: (i) developing hormonal methods of EC that are more effective and better tolerated; (ii) determining effectiveness and mechanism of action; and (iii) improving accessibility.

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## Methods of emergency contraception

### *Ethinyloestradiol in combination with levonorgestrel*

The first method of emergency contraception to be described was a high dose of oestrogen taken over 5 days. It caused significant vomiting and was

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largely superseded by the so-called Yuzpe regimen of EC – 100 μg ethinyloestradiol in combination with 0.5 mg levonorgestrel taken twice with the two doses separated by 12 h[1]. This regimen, recommended for use within 72 h of unprotected intercourse, is the method that has until very recently been used in the industrialised world. In the UK, it is marketed as Schering PC4®. A relatively high dose of oestrogen, the regimen is also associated with nausea (in some studies almost 50% of women complain of nausea), but has the enormous advantage of being readily available in the form of commonly used combined oral contraceptive pills (*e.g.* Ovran®) which have been used in some countries where there has been no licensed product[2].

### *Levonorgestrel*

Although used in some Eastern European and non-industrialised countries for many years, an EC regimen consisting of levonorgestrel (LNG) without oestrogen was largely ignored until the mid-1990s. Two trials[3,4] comparing the Yuzpe regimen with levonorgestrel, 0.75 mg twice with the two doses separated by 12 h, have been published. The first,[3] involving 834 women, was randomised but not double-blinded, and demonstrated that levonorgestrel was as effective (although not significantly more effective) than the Yuzpe regimen if used up to 48 h after intercourse. Hardly surprisingly, since it is the oestrogen which causes the nausea and vomiting, LNG had significantly fewer side-effects. A larger randomised double-blinded multicentre study[4] involving 1998 women demonstrated that LNG was significantly more effective than the Yuzpe regimen (85% of expected pregnancies were prevented by LNG compared with only 58% by the Yuzpe regimen). This study confirmed the better tolerability of LNG. It also demonstrated[5] that both LNG and the Yuzpe regimen were more effective the sooner after intercourse they were used (Table 1). On the basis of these two studies, licensed products became available in France (Nor-Levo®) and the US (Plan B®) in 1999 and in the UK in 2000 (Levonette-2®) LNG is likely to become the method of choice of the early 21st century.

**Table 1** Percentage of expected pregnancies prevented in relation to the delay between intercourse and time of treatment with emergency contraception (data from WHO[5])

| Time of treatment | LNG | Yuzpe |
|---|---|---|
| Within 24 h | 95 | 77 |
| 24–48 h | 85 | 36 |
| 48–72 h | 58 | 31 |

### *Mifepristone*

The most promising hormonal emergency contraceptive is the antiprogesterone, mifepristone. Two randomised controlled trials[6,7] compared a single dose of 600 mg mifepristone taken within 72 h of intercourse with the standard Yuzpe regimen. In one[6], there were no pregnancies among 402 women taking mifepristone, while in the other[7] there were 3 pregnancies among 195 women, but all conceived 10–15 days after mifepristone had been given. Both studies concluded that mifepristone was more effective than the Yuzpe regimen and significantly better tolerated. However, it was much more commonly associated with a delay in the onset of menses, a major concern for women waiting for menstruation to indicate that they are not pregnant. None of these findings should have come as a surprise, since it was already clear from its use as an abortifacient that mifepristone is extremely well tolerated and, from a variety of studies, that it would inhibit both ovulation and implantation[8] and, therefore, would be effective as a post-coital agent at whatever stage of the cycle it was taken. Any delay in ovulation would inevitably be associated with a delay in the onset of the next menstrual period.

Hypothesising that a lower dose of mifepristone would be just as effective as an emergency contraceptive, but perhaps with less disruption of cycle length, the World Health Organization (WHO)[9] undertook a randomised trial of three different doses of mifepristone 600 mg (559 women), 50 mg (560 women) and 10 mg (565 women). There was no significant difference in effectiveness between the three doses, 84–86% of expected pregnancies were prevented. Mifepristone was effective up to 120 h (5 days) after intercourse and, in contrast to LNG and the Yuzpe regimen, there appeared to be no decrease in efficacy with time. There were no major side-effects, overall 17.4% of women complained of nausea, and the delay in the onset of the next menses was significantly ($P < 0.01$) related to the dose of mifepristone. A delay of more than 7 days occurred among 36% of women treated with 600 mg mifepristone, 23% treated with 50 mg and 18% with 10 mg.

A randomised double-blinded comparison of mifepristone and levonorgestrel is underway and the results should be available by 2001.

Although possibly the best method tested so far, mifepristone is unlikely to become widely available as an emergency contraceptive in the foreseeable future (except in China where it is the method of choice) because it is known to be an abortifacient. Its development as a contraceptive has for many years been the victim of anti-abortion politics, it is also expensive.

### *Other methods*

Other compounds have been tested as emergency contraceptives. Interest increased in the antigonadotrophin danazol in the late 1980s, but waned after the publication of one trial[6] (discontinued prematurely) suggesting that it was ineffective.

The IUD is the most effective method (for review see Trussell and Ellertson[10]). It prevents over 95% of pregnancies and can be used up to 5 days after the earliest estimated day of ovulation. Insertion requires trained personnel and is invasive.

## Efficacy of emergency contraception

There has never been a placebo-controlled trial of any method of emergency contraception, nor, with the exception of mifepristone[9], have any dose finding studies yet been published. In recent years, it has become accepted practice to express the effectiveness of an EC as the proportion of expected pregnancies it prevents. The expected number of pregnancies is estimated by multiplying the number of women who had unprotected intercourse on each cycle day by an estimate of the probability of conception on that day and then summing over all cycle days[11]. In recently published estimates of efficacy, the possibility of conception for each cycle day has been taken from data collected by Wilcox and colleagues[12]. Using this method, the WHO reports that mifepristone and LNG both prevent 85% of pregnancies – each estimate on the basis of only one trial. Using data from eight different trials, Trussell and colleagues[13] estimate that the Yuzpe regimen prevents at least 74% of pregnancies and probably more. It should be emphasised, however, that these figures are only estimates and that there are some problems with the method used to calculate them. Firstly, data used to calculate the probability of conception for each cycle day come from prospective studies of women actively trying to achieve a pregnancy and keeping written records of menstrual bleeding and coitus. Many women seeking emergency contraception have been trying – albeit, some of them, rather half heartedly – to avoid pregnancy. Many present following a burst or slipped condom and are not sure whether seminal fluid leaked into the vagina, but prefer to err on the side of caution. Most do not keep written records of menstruation and the date of their last menstrual period (LMP) is usually an estimate, and not infrequently a complete guess. Although investigators undertaking clinical trials try to pin women down to an accurate LMP date, an error of only one day makes a significant difference to the probability pregnancy. Regular cycles too often vary in length by 2 days in either direction and the exact day of ovulation will vary from month to month. Thus, calculation of the cycle day when intercourse occurred is rarely accurate. In our own trial[6] of mifepristone *versus* the Yuzpe regimen of EC, plasma progesterone or urinary pregnanediol was measured on the day of treatment providing the opportunity to determine whether the cycle data were compatible with the biochemical evidence of ovulation. Of 368 women, 51% believed to be in the mid-luteal phase of the cycle had a progesterone/pregnanediol value

indicating that ovulation had not occurred, while 21% of 205 women thought to be in the mid-follicular phase had biochemical evidence of ovulation. Although not commented upon in the publication, other studies[7], in which progesterone have been measured, show similar discrepancies. Estimates of efficacy also depend for their accuracy on the assumption that, if a pregnancy does occur, it does so as the result of the act of coitus for which EC was used. This is often not the case; women have often had more than the one act of intercourse for which they seek treatment and they have intercourse during the days following treatment. In the WHO dose finding study of mifepristone[9], in the group given 600 mg mifepristone, 4 of the 7 women who conceived did so at least 15 days after treatment. Even in trials where data are collected, it is not possible to determine which of two (or more) acts of coitus are responsible for conception unless they are separated by at least 7 days and only then if accurate ultrasonography is performed in early pregnancy. In the WHO multicentre trial of LNG *versus* the Yuzpe regimen of emergency contraception[4], women who had intercourse after receiving EC (whether with or without a barrier method) had higher pregnancy rates than women who did not. In this study, almost 10% were already pregnant when they took emergency contraception and, in another 10%, pregnancy status was unknown. Indeed, when women who were, or who may have been, pregnant at the time of treatment and those who had had further acts of intercourse were excluded from the analysis, the proportion of pregnancies prevented increased from 85% to 89% in the LNG group but by 19% (from 57% to 76%) in the Yuzpe group and the difference between the two methods was no longer statistically significant.

## Mode of action

There is good evidence from a number of sources to show that mifepristone inhibits ovulation and implantation[8]. Its precise mechanism of action, when it is used as an EC, depends on when in the cycle it is taken[14]. In contrast to LNG and the Yuzpe regimen, the efficacy of mifepristone does not decrease with time since coitus[9]. If a method works by inhibiting implantation, then it should be effective up to perhaps 7 days after ovulation.

There are, as yet, no published data on the mechanism of action of LNG used as an emergency contraceptive. Several biomedical studies have demonstrated convincingly that the Yuzpe regimen can delay or inhibit ovulation[15,16]. Some have demonstrated minor changes in the endometrium which, the authors speculate, may be sufficient to inhibit implantation[17]. However, the group with the greatest expertise and track record in research on the endometrium were unable to demonstrate any effect which might

be associated with the inhibition of implantation[15]. Some argue that the Yuzpe regimen could not be as effective as it appears to be, if it worked only by preventing or delaying ovulation. A recent review used sophisticated mathematical calculations to demonstrate that some mechanism other than the prevention of ovulation must account for 13.38% of the estimated efficacy of the Yuzpe regimen[11]. Since LNG appears to be much more effective (albeit in only one trial), one has to conclude that it too must do more than simply inhibit ovulation. Of course conclusions on mechanism of action drawn from efficacy estimated from inaccurate data may not be very robust.

There are, of course, other possible mechanisms which would reduce the chance of conception – inhibition of fertilisation or alteration of tubal motility for example. Although it is possible that available methods of EC work through a number of different mechanisms, there is no good evidence available. What can be said is that neither the Yuzpe regimen nor levonorgestrel alone will be effective after implantation has occurred. Mifepristone, in contrast, will be effective after implantation in up to 60% of women if 600 mg is taken, but it is unlikely that 10 mg would act as an abortifacient.

## Safety

The safety of the Yuzpe regimen of EC has long been a topic for discussion mainly because of a tendency to extrapolate from data associated with the combined pill (COC). The main concern has been cardiovascular disease and particularly venous thrombo-embolism (VTE), as the total dose of ethinyloestradiol (200 mg) is 6 times that of a single low dose COC tablet. There are very few data on safety and much of what can be said stems from clinical experience and common sense.

Even with long-term use of the combined pill, the risk of MI and stroke is extremely small[18] and the risk associated with PC4 can be disregarded. Because of concerns about the association between migraine and cerebrovascular accident, it is sometimes suggested that Schering PC4 should not be taken during an attack of focal migraine[19]. There is no evidence for this advice, but where LNG is available for emergency contraception this would be the method of choice.

There has only been one biochemical study of the direct effects of PC4 on clotting factors[20] and no effect was identified. Schering PC4 was licensed in 1984 and by July 1996 (when the data were last reviewed[14]) it had been used more than 4 million times. Few adverse events have been reported to the Committee on Safety of Medicines (CSM) in the UK: 115 reports of 159 reactions (some women having more than one), included 61 pregnancies. Only three cases of venous thrombosis had been reported, and in none is the relationship between emergency contraception and the event clear-cut.

In a study using the GP research database in the UK[21], the records of over 73,000 women who had between them received over 100,000 prescriptions for Schering PC4 over an 8 year period between 1989–1996 were reviewed. No women had a venous thrombotic event within 60 days of using PC4. During the period of study, the same cohort of women experienced a total of 19 cases of VTE, 5 during pregnancy or the postpartum period, 8 during COC use and 6 cases without exposure to endogenous or exogenous oestrogens. The relative risk of VTE (compared to the spontaneous incidence of VTE) was 1.7 for second generation COCs, 3.7 for third generation COC and 5.6 for pregnancy/postpartum. The study concluded that PC4 use was not associated with an increased risk of VTE.

Both the WHO (which added the Yuzpe regimen to its essential drugs list in 1996) and the International Planned Parenthood Federation have stated that there are no absolute contra-indications to the Yuzpe regimen except known pregnancy. If it is inadvertently used in the presence of an on-going pregnancy, it will almost certainly do no harm. Reliable data on the outcome of pregnancy after failed PC4 are lacking, but the lack of demonstrable teratogenicity of the COC and the timing of the administration of emergency contraception (long before organogenesis starts) are reassuring[22,23]. Thus, the regimen is only contra-indicated because it does not work once pregnancy is established, not because it is known to be harmful.

There are few data on the safety of LNG used as an emergency contraceptive. In the two published studies[3,4] there were no serious adverse events, but follow-up ended once menstruation had occurred or if a pregnancy was diagnosed. It seems extremely unlikely that LNG used in this manner would have any serious side-effects. The compound has been used for many years in a large number of contraceptive preparations and is prescribed in doses of up to 15 mg a day for 12 days (or longer) each month and for months on end for the management of anovulatory dysfunctional uterine bleeding and menorrhagia. Mifepristone too has an extremely reassuring safety profile with no serious risks associated with its use.

## Accessibility of emergency contraception

It has been calculated that the wide-spread use of EC could prevent millions of unwanted pregnancies[24]. Although recent interest in EC has led to its inclusion as part of routine family planning services in many countries, it is still not widely used. The barrier to lack of use is not lack of an effective, acceptable and safe method, but rather to lack of knowledge and difficulties with access. Although knowledge in some countries has improved in recent years[25,26], particularly among young

women who are perhaps most likely to use EC, still very few women have ever used EC. Data are available from nationally representative surveys in Nigeria and the US where less than 1% of women have used EC and in Finland where 4% have used it[27]. In the UK, where perhaps the population is the most knowledgeable and where it has been available for over 15 years, it has been estimated that around 12% of women have ever used it[28]. Access to EC is limited because of ignorance and confusion among both providers and potential users. EC is a controversial therapy, which is often confused (sometimes deliberately) with abortion. As discussed earlier there is misplaced concern about its safety because it is confused with 'the pill'. There are also concerns about possible abuse or misuse (including repeated use) and warnings that its wider availability might encourage promiscuity, unsafe sex and the abandonment of other conventional methods of contraception. In reality what little data exist are re-assuring. In the UK, only 6% of women who have used EC have used it more than 3 times[28] and in Finland women who had used EC were no more likely to have had an abortion than women who had never used it[29]. In a pilot study[30] in which 553 women were given a supply of EC to keep at home and their pattern of contraceptive use over 1 year of follow-up was compared with women who had to see a doctor to get EC, easier access to EC did not result in repeated use or in women abandoning more effective methods of contraception.

In many countries, including the UK, accessibility is limited because EC must be prescribed by a doctor and the 72 h rule makes that difficult. Recognising that EC is safe and that the benefits of easier access almost certainly outweigh the risks, the close of the 20th century is witnessing attempts to improve access. The most effective way to do this would be to make EC available off prescription. In the West, only France has done this, a levonorgestrel product was approved as a pharmacy medicine and went on sale in 1999. In the US in 1998, pharmacists in Washington State (and subsequently in over 20 other states) were encouraged to arrange collaborative prescribing agreements with physicians so that they could provide EC directly to women without the need for their seeing a doctor. In the UK in 1999, the British Pregnancy Advisory Service (a privately funded abortion provider) made EC available for sale in their clinics following consultation with a nurse or doctor. It is highly likely that Levonelle-2® will become available with prescription in the UK in early 2001.

It remains to be seen whether improved access to EC leads to increased use and, thereby, to a reduction in unwanted pregnancy. In the Edinburgh study[30], advanced provision of EC was associated with a non-significant reduction in the risk of unwanted pregnancy (RR 0.67; 95% CI, 0.4–1.2). A much larger on-going trial in which all women between the ages of 16

and 29 years living in one health board area of Scotland (over 85,000 women) are being offered supplies of EC to keep at home[31] should help to answer this question, but results will not be available until 2002.

## Key points for clinical practice

- Emergency contraception can prevent unwanted pregnancy
- Levonorgestrel 0.75 mg twice separated by 12 h may be more effective that the Yuzpe regimen and is better tolerated
- Levonorgestrel and the Yuzpe regimen are more effective if used within 24 h of intercourse
- Mifepristone may well be the most effective oral method
- Effectiveness of emergency contraception cannot be determined precisely but all methods prevent at least 75% of pregnancies
- Use is limited by difficulty with access and the need to see a doctor
- Advanced provision of emergency contraception is safe, sensible and may reduce abortion rates

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# Case Studies in Emergency Contraception From Six Countries

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In countries where emergency contraception is offered, its availability and use vary widely, according to such factors as regulations and policies regarding the method, providers' and women's understanding of and attitudes toward it, and cost. The experiences with the method in six countries—the United Kingdom, the Netherlands, Malaysia, China, Mexico and Nigeria—illustrate a range of issues involved in introducing and encouraging the acceptability of emergency contraception.

Emergency contraception first became available in most of these countries in the late 1960s and early 1970s. Today, in the United Kingdom and the Netherlands, the method is an accepted part of family planning practice and is well-known among doctors and women. This acceptance may be partly due to the method's inclusion in the health insurance systems of these countries.

Another factor explaining the established role of emergency contraception, at least in the Netherlands, is the lack of moral debate surrounding the method. Only its side effects and efficacy seem to engender controversy; the need for emergency contraception is acknowledged and accepted even for teenagers, for whom sexual activity is socially sanctioned.

By contrast, in Malaysia, as in other countries where abortion is strictly regulated, emergency contraceptive methods are marketed legally, but family planning organizations shy away from offering them.

In China, postcoital methods have long been offered by the government family planning service. However, these methods have not been separated into those advocated for emergency use only and those recommended for ongoing use.

Finally, in Mexico and Nigeria, awareness of emergency contraception continues to be low among both health care providers and the public.

Research, both on a way to create knowledge of emergency contraception and on a way to publicize the methods, has been largely concentrated in European countries; many developing countries, and even many developed ones, have yet to conduct any research on this topic. For example, Mexico's first clinical trial of an emergency contraceptive method (a combination of levonorgestrel and ethinyl estradiol, administered orally or vaginally) is under way, fully 30 years after the original research on the method was conducted.

In the case studies that follow, we summarize information on experiences with emergency contraception in each of these countries. We then draw on these experiences to suggest lessons for other countries seeking to introduce or expand the use of this method.

## United Kingdom

### *History of Emergency Contraception*

Although British doctors occasionally administered high-dose estrogen or inserted an IUD for the purpose of emergency contraception in the early 1970s, it was not until 1974 and the publication of the first article on emergency contraception using a combined estrogen-progestogen regimen that the method's use became widespread in the United Kingdom.[1] The National Association of Family Planning Doctors met in 1982 to discuss emergency contraception and a year later published a set of clinical guidelines establishing two combined pills, Ovran and Eugynon 50, as the preferred hormonal regimens.[2]

In 1982, the Department of Health stated that treatment up to 72 hours postcoitally was "probably legal," but that treatment after five days "might be considered an abortion."[3] The following year, an antiabortion lobbying group filed several complaints against clinics providing emergency contraception; the group based its argument on the Offences Against the Person Act of 1861, which made it illegal for a woman or her doctor to "intend to procure a miscarriage." In response, the attorney general ruled that emergency contraception administered within 72 hours after intercourse was not a criminal offense, reasoning that "preventing implantation is not procurement of a miscarriage."[4]

At the request of the Department of Health, the Committee on Safety of Medicines undertook a review of emergency contraception in 1983 and determined that the method was "acceptably safe for occasional use." The pharmaceutical company Schering submitted an application for a product based on Eugynon 50 to the Medicines Division in August 1983 and received a license in January 1984. PC4 (50 mcg of ethinyl estradiol and 0.5 mg of norgestrel in each of four tablets) was on the market by October 1984.

Discussion is under way with regard to making PC4 available from pharmacists without a doctor's prescription, a step that most professional organizations support. The Royal College of Obstetricians and Gynecologists organized meetings about the matter in December 1994 and July 1995. It is up to Schering to apply to change the license, and the company thus far seems reluctant to do so.

### *Availability and Prevalence*

General practitioners are the major source of emergency contraception in the United Kingdom. Everyone in the United Kingdom is entitled to register with a general practitioner. For contraceptive services, women may also visit a general practitioner other than the one they are registered with, although this option is not widely known.

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[4]Abortion is legal in the United Kingdom under the terms of the 1967 Abortion Act, which requires agreement by two doctors that a woman has grounds for terminating a pregnancy. A report of the abortion, signed by the two doctors and specifying the grounds for termination, must be made to the Department of Health.

Women in most cities and large towns may also seek emergency contraception at National Health Service family planning clinics. Since 1972, these clinics have provided contraceptives free of charge. The clinics offer anonymity to women reluctant to consult their general practitioner and may be open in the evenings and on weekends; however, not all towns—and few villages—have such centers, and at least half of these clinics are open only once a week.

The nonprofit Brook Advisory Centres, which provide services to young people in cities throughout England and in Edinburgh, Scotland, provide emergency contraception. Some hospitals' accident and emergency departments also provide hormonal emergency contraception.

National data on the prevalence of emergency contraception do not exist, but reports from clinics suggest that use has been rising rapidly. Knowledge of emergency contraception is fairly high; surveys from the late 1980s found that 65–75% of women undergoing induced abortion had heard of emergency contraception.[5] A small, unpublished survey conducted by Schering in 1994 found that 90% of women had heard of emergency contraception. However, many women continue to be unaware of the 72-hour time limit or of the method's ready availability. Levels of knowledge of postcoital IUD insertion are low.

Schering's sales data for PC4 indicate that about 353,700 packets were sold in 1992, and 420,500 were sold in 1993. Schering has sold 2.5 million packets of PC4 since the regimen was licensed in 1984. One clinic in Edinburgh reports that the use of emergency contraception has doubled in the last five years and now accounts for about 4% of the 47,000 visits made to the facility annually.

There is no way of estimating the extent to which Ovran is prescribed for emergency contraception or how many IUDs are inserted for postcoital indications, since these contraceptives are also used on an ongoing basis.

### *Cost*

All contraception in the United Kingdom, including emergency contraception, is free to the patient. Schering sells the PC4 combination to the National Health Service at a cost of about U.S. $2.20 per treatment. Many family planning clinics and some general practitioners make up their own supplies using Ovran, at a cost of about 25 cents for the four tablets. The actual cost to the clinic is somewhat higher because of packaging costs. In addition, some clinics provide six tablets, to leave a woman with two spares in case she vomits. Others add an antiemetic, at a cost of around 16 cents per tablet. An IUD costs the National Health Service about $11–$16, although clinics that buy in bulk may pay considerably less.

A recent study of the cost-effectiveness of contraception estimated considerable savings to the National Health Service from the use of emergency contraception to prevent unintended pregnancy.[6] Even on the basis of failure rates as high as 25 births per 100 users of emergency contraception per year, the study estimated that prescribing PC4 costs between $19 and $74, depending on the provider, and saves the government health service $727–$806. Estimates of costs averted did not include such costs to society as those associated with education and social services.

## Netherlands

### *History of Emergency Contraception*

Emergency contraception has been used in the Netherlands since 1964[7] and is widely known and accepted there. The Netherlands places a high priority on preventing unwanted pregnancy, and information on emergency contraception has always been included in family planning education programs and materials. The level of contraceptive use is generally high, and the incidence of unwanted pregnancy and abortion is low. Thus, while emergency contraception is free of moral debate, is not considered an abortifacient and is considered acceptable for teenagers, the need for it is reduced by the high levels of effective contraceptive use among women of all ages.[8]

As early as 1970, emergency contraception was covered in the first family planning handbook for Dutch doctors,[9] and within a few years, the method became widely available through general practitioners, who form the backbone of the Dutch health care system. (Every citizen is registered with a general practitioner.) The Dutch Family Planning Association, the Rutgers Stichting, also began offering the method in the early 1970s. However, overall use of emergency contraception declined by 50% between 1974 and 1983, primarily because of a sharp increase in the use of ongoing methods of contraception after their inclusion in the national health insurance program.

The original emergency contraception regimen used in the Netherlands consisted of five pills of ethinyl estradiol taken for five days—a total dosage of 25 mg, or the equivalent of three years' worth of modern low-dose oral contraceptives. (This regimen is commonly known as the 5x5 method.) In around 1980, the "Yuzpe method" was introduced in the Netherlands. This regimen, which came to be known as the 2x2 method for its two doses of two pills taken 12 hours apart, quickly replaced the 5x5 method; for example, by 1985, 83% of prescriptions for emergency contraception from general practitioners[10] and 97% of those from the Rutgers Stichting were for the Yuzpe method.[11] However, over the last 10 years, the side effects and efficacy of both methods have been the subject of vigorous debate among practitioners and researchers. Several specialists feel that the 5x5 method provides far too heavy a hormonal dose, while others are of the opinion that the 2x2 method is not sufficiently reliable.

This debate has spilled over into the general public's consciousness and has at times affected the willingness of physicians to prescribe certain regimens and of women to use them. The 5x5 method, sometimes referred to in the mass media as a "hormonal bomb," has been subjected to particularly harsh criticism. After articles critical of the method were published in 1987, the number of emergency contraception prescriptions written by general practitioners fell by 25% from the year before.[12] Today, some doctors reportedly prescribe their own emergency contraception regimens,[13] and some women devise their own.

In response to this controversy, in 1987, the Rutgers Stichting adopted a policy of offering women a choice of the 5x5 or the 2x2 regimen or IUD insertion. More recently, there have been calls to make mifepristone available for emergency contraception in the Netherlands.[14]

### *Availability and Prevalence*

Partial data on use of emergency contraception in the Netherlands are available through 1991, collected as part of the national sentinel system of general practitioners. General practitioners provide about three-quarters of the prescriptions for emergency contraception in the Netherlands; in 1991, they wrote 28,000 emergency contraception prescriptions.[15] This level had remained more or less stable since 1985. The Rutgers Stichting probably provides an additional 2,000–7,000 prescriptions annually. Data on IUD insertion for emergency contraception are not available, although use of this method is presumed to be rare because most women requesting emergency contraceptive services are young and have never been pregnant. In total, the rate of use is

about one per 100 women per year.

In 1991, of all women receiving emergency contraception from general practitioners, about 70% were younger than 25, and 34% were younger than 20.[16] The proportion of emergency contraception prescriptions that are for adolescents, however, is higher (51%) at the Rutgers Stichting clinics.

A pair of studies conducted in Amsterdam[17] suggest that condom failure prompted the request for emergency contraception in 19–29% of cases and that missed pills accounted for 13–25% of requests. Slightly fewer than half of the women in these studies had had unprotected intercourse at midcycle, suggesting that many women seek emergency contraception even when the risk of pregnancy is slight.

*Cost*

The cost to a Dutch woman of emergency contraception is determined by the type of health insurance that covers her. The largest insurance carrier is the Sick Fund, which is publicly controlled but privately administered and covers about 60% of all citizens. The remaining 40% of citizens are privately insured. In addition, all Dutch citizens are covered by the General Law on Exceptional Medical Cost (AWBZ), a national form of insurance intended primarily to cover catastrophic and long-term care, but recently expanded to include the cost of medical drugs. Sick Fund members may receive medication free of charge directly from their pharmacy. Privately insured patients must pay for medications out of pocket, but can be reimbursed by the AWBZ.

At pharmacies, the price of the 2x2 method is about $7–$9. The 5x5 method, including an antinausea medication, costs around $41. In order to receive the prescription, however, women must consult their general practitioner. This visit is free for women covered by the Sick Fund; privately insured women must pay a fee of approximately $20.

The Rutgers Stichting provides the 2x2 regimen free, but charges a consultation fee that varies from around $10 to $20, depending on whether the woman is older than 18. Women who obtain the 5x5 method from the Rutgers Stichting pay about $20 for the pills and antinausea medication, in addition to the consultation fee.

Both the Sick Fund and the private insurance system may impose obstacles for adolescents. Young people must either request the Sick Fund card from their parents or pay directly and then request reimbursement, through their parents, from the AWBZ. Consequently, many adolescents seek emergency contraception at the Rutgers Stichting clinics rather than from their general practitioners.

## Malaysia

*History of Emergency Contraception*

Although hormonal emergency contraception has purportedly been available in Malaysia since 1966, the first emergency contraception regimen, Postinor, was not officially registered there until 1987. Three years later, a second regimen, Estinor, was registered. These are reportedly the most common specifically registered methods used.

Both brands consist of 0.75 mg tablets of levonorgestrel, and the recommended dose is a single tablet to be taken within one hour after unprotected intercourse. If the woman has engaged in more than one act of intercourse, the manufacturers recommend that a second dose (two Postinor tablets or one Estinor) be taken eight hours later. These brands are usually sold in 10-tablet strips, and physicians often divide strips and provide women with only as many pills as they need.

In Malaysia, emergency contraception is often erroneously viewed as an "abortion pill." Since abortion is stringently regulated, this misperception may have led to reluctance on behalf of some service providers and program administrators to provide emergency contraception or even information about its existence and benefits.

*Availability and Prevalence*

Data on emergency contraception are not available from the national family planning program, and the literature on the method in Malaysia is scant. Government-run family planning clinics do not provide emergency contraception, and the private practitioners who do are reluctant to speak about it. Although the Federation of Family Planning Associations, Malaysia (FFPAM) prefers to stress regular use of an effective method, rather than distributing something that acts as an "abortion pill," FFPAM members follow guidelines for the provision of emergency contraception established in a 1992 International Planned Parenthood Federation quality assurance manual.[18]

Emergency contraception is, however, available from both pharmacies and private physicians in Malaysia. Although Postinor and Estinor both fall under the regulations of the Poisons Act, they may be purchased without prescription if the woman provides her name, address and identification card number to the pharmacist.

Very rough estimates based on sales by pharmacies indicate that at least 20,000 women obtained emergency contraceptives in 1994. The exact number is difficult to determine because some women purchase just the tablets they need to cover one act of unprotected intercourse, whereas others buy extra pills.

Few women receive emergency contraception from FFPAM clinics; only 60 did so in 1993. These women were 20–40 years old and requested emergency contraception for a variety of reasons: unexpected and unprotected intercourse, missed pills and ruptured condoms. In addition, some pharmacies report that Estinor is used by sex workers, as well as by rape victims.

At pharmacies in Malaysia, the strip of 10 pills—enough to cover five episodes of unprotected intercourse—costs the purchaser $3–$6. At private clinics, the cost for 1–3 tablets is approximately $4, which includes the consultation fee.

## China

While postcoital contraception is a topic of research for China's State Family Planning Commission program, and postcoital methods are included in the government family planning program, figures on the prevalence of emergency contraceptive use are not available.

Postcoital contraception was first developed in China in the 1970s, primarily for use by married couples living at a distance from one another. Thus, the focus of postcoital contraception has been on a "visiting pill" for ongoing use by couples who are only infrequently exposed to the risk of pregnancy. Although the literature on the use of visiting pills is extensive, there are few reports of their use for emergency contraception.

Preparations packaged as visiting pills (also known as vacation pills and quick-action pills) often consist of high doses of norethisterone, megestrol acetate or norgestrel. Other compounds, such as quingestanol, norgestrienone and norethisterone acetate-3-oxime, are also used.[19]

The most commonly used visiting-pill formulation is anordrin, a compound synthesized in Shanghai in 1975.[20] One 7.5 mg tablet is taken the morning after unprotected intercourse, and one is taken every night for three nights. The cost of the regimen is only a few cents.

Reportedly, some women obtain IUDs after experiencing contraceptive failure (for example, when a condom has broken), but it is difficult to distinguish when an IUD has been inserted for emergency contraception.

Researchers at the International Peace

Maternal Hospital in Shanghai have experimented with levonorgestrel suppositories, in the hopes that vaginal administration would reduce the nausea and vomiting associated with the elevated hormonal dosage of emergency contraception. The tablets, however, were not sufficiently soluble to be highly effective.

China is also testing mifepristone as an emergency contraceptive, both alone and in conjunction with other hormones. As yet, mifepristone is available only in clinical trials, but family planning advocates hope it will be introduced soon for general use as an emergency contraceptive.

## Mexico

Emergency contraception is little known in Mexico, among either providers or consumers. Since oral contraceptives are available without prescription, women have potential access at least to the Yuzpe regimen (which would cost about 50 cents); however, they may not be aware of it.

Although requests for emergency contraception reportedly are frequent in Mexico, providers themselves lack adequate information on this method. One objective of a clinical trial currently under way in Mexico is to increase knowledge of emergency contraception among health professionals, including family doctors and general practitioners, and pharmacists.

## Nigeria

Traditional fertility control methods in Nigeria include several that are used either immediately after unprotected intercourse or when a pregnancy is first suspected. Among these are potash mixed with bluing, lime taken in high concentration with cayenne pepper seeds, and a codeine tablet used together with illicit gin. Nigerian women are also gradually learning that altered doses of oral contraceptives can function as emergency contraceptives.

No data are available on the prevalence of emergency contraception or on the costs of hormonal regimens in Nigeria. An IUD insertion costs $23 in a private hospital. Codeine and gin costs about $2.25; the other traditional emergency contraceptives are very inexpensive.

## Lessons Learned

The experiences with emergency contraception described in this article highlight several issues that may be relevant in other countries as well.

As the case studies demonstrate, both providers and potential users need to be well informed about emergency contraception, how it is used and its availability. The importance and the role of emergency contraception can easily be overshadowed by family planning's traditional mission to ensure consistent, effective contraceptive use, particularly in developing countries, where the focus may be on lowering fertility.

Emergency contraception is most widely used in countries where it is well integrated into general family planning services and information and education efforts, such as the United Kingdom and the Netherlands. It has a key place both within family planning's traditional emphasis, as a backup for method or user failure, and as a last resort in the instance of unexpected intercourse.

Another lesson is that a clear distinction must be drawn between emergency contraception and abortion, especially in countries where abortion is legally restricted or carries a moral stigma. A confusion of emergency contraception with abortion can seriously impede efforts to prevent unintended pregnancy through use of emergency methods, as in Malaysia. Emergency contraception should be cast as an important way to reduce the need for abortion.

Furthermore, the experiences in the United Kingdom and the Netherlands illustrate that even in countries that have good data on emergency contraception, information about its use is incomplete. Data on emergency contraception should be collected along with other routine family planning statistics. To date, efforts to examine the use of emergency contraception have been complicated by the fact that the IUD and combined oral contraceptives may be used for either regular or emergency contraception. In the future, efforts should be made to distinguish the different uses of these methods.

The case studies also show that emergency contraception should be available from a variety of sources—certainly general practitioners or family doctors, as well as family planning clinics, which offer more anonymity. The British and Dutch experiences demonstrate the importance of both a network of highly informed, properly motivated, easily accessible service providers and wide dissemination of information among them and the lay public. While the success of emergency contraception in these countries probably cannot be separated from the overall high quality and accessibility of their health care and contraceptive services, it appears that emergency contraception is most widely used when it is well integrated into routine care.

A further point for planners to consider is that there is more than one way to administer emergency contraception; countries might experiment with different delivery mechanisms and regimens, as China has done and as Mexico plans to do in its current study.

The remaining lessons concern uses of emergency contraception that have not traditionally been the focus of most Western countries. For example, as China has demonstrated, emergency contraception may have applications beyond preventing pregnancy after a single exposure to unprotected intercourse. Methods like the visiting pills used in China may well be appropriate for use in other countries where couples have intercourse infrequently. In Malaysia, meanwhile, the reported use of Estinor by sex workers suggests another group for whom emergency contraception may be particularly valuable.

Finally, the Dutch case reveals that emergency contraception may be particularly important for adolescents. As young people establish their sexual identity and contraceptive practice, they may be likely to use contraceptives ineffectively and subsequently experience contraceptive failure. For them, emergency contraception may provide a crucial safety net in the event of intercourse they did not expect or adequately prepare for, as well as a bridge to more regular and sustained contraceptive use.

## Conclusion

Although emergency contraception has been available for about three decades, its potential to reduce the incidence of unintended pregnancy and abortion is just beginning to be realized. In only one of the six countries examined here, the Netherlands, has the method settled into a well-accepted niche so that efforts can focus on refining the regimens and informing women about them. Even in the United Kingdom, the use of emergency contraceptives has been growing rapidly, which suggests that the method is still regarded as "new."

Emergency contraception may well fill an important gap among groups whose needs have gone unmet by traditional family planning programs. The experiences of these six countries suggest that family planning researchers and practitioners must be both persistent and innovative as they work to make emergency contraception available to more women in more countries around the world.

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# LETTERS

## Unmet Need and Potential Demand

A digest entitled "Developing Countries Show Sizable Cross-National Variations in Unmet Need, Demand for Contraception," summarizing a Demographic and Health Surveys comparative report [21:161–162, 1995], gave a misleading picture of the actual situation. Instead of the term "demand for contraception," the phrase "potential demand for contraception" would have been better. Demand for contraception was defined as a combination of current use and unmet need, but (as the digest pointed out) many women categorized as having an unmet need for contraception do not intend to use any contraceptive method. Their reasons are varied, and include ambivalence about childbearing, a lack of information about methods, fear of health effects, or personal or spousal opposition to family planning. To classify such women as having a demand for contraception is very misleading.

Further, the digest mentions that "some women classified as having an unmet need for family planning were not sexually active in the month before the survey." Except for the possibility of rape, sexual abstinence is a perfectly effective contraceptive method, and attributing a demand for contraception to such women overstates the case.

Both a real demand for contraception and an important level of unmet need exist in developing countries. However, to state that women who are not practicing contraception for lack of information or motivation are actually demanding it can mislead policymakers into ignoring the great need for information and motivation in addressing the reproductive health needs of women and men worldwide.

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***The editors reply:***

Our intention when we digest a published piece of research is to report the study's findings as accurately and completely as possible. Since the Demographic and Health Surveys report on which this digest was based used the terminology "demand for contraception" throughout, so did we. The author of the original report agrees, however, that "potential demand" probably represents an improvement over "demand."

ELSEVIER

Contraception

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# The effects of peri-ovulatory administration of levonorgestrel on the menstrual cycle☆

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**Abstract**

Levonorgestrel (LNG) 0.75 mg administered 12 h apart within 72 h of unprotected coitus, is an established method of emergency contraception (EC). The mechanism of action of LNG used in this manner is unknown. We administered LNG 0.75 mg twice immediately before ovulation, to test the hypothesis that LNG acts as an emergency contraceptive by abolishing the pre-ovulatory lutenizing hormone (LH) surge and thereby delaying ovulation. Twelve women took LNG on or before the day of the first significant rise in urinary LH in 12 cycles. In four women, the LH peak and the onset of next menses were significantly delayed (delay of 16.8 days (SD ± 8.7) from the day of mean LH peak in placebo cycles). One woman did not ovulate at all, despite a normal LH peak and cycle length. In the remaining eight women, LNG did not affect ovulation or the cycle length, but the length of the luteal phase and the total luteal phase LH concentrations were significantly reduced. We suggest that LNG acts as an emergency contraceptive by other mechanisms as well as delaying the LH surge and interfering with ovulation. 

*Keywords:* Emergency contraception; Levonorgestrel; Mechanism of action

## 1. Introduction

Levonorgestrel (LNG) 0.75 mg administered twice with the two doses 12 h apart has been shown to be an effective method of emergency contraception (EC) when used within 72 h of unprotected intercourse [1,2]. Although the regimen is now licensed in the UK, USA, and throughout much of Europe and is widely regarded as the emergency contraceptive method of choice [3], the mechanism of action remains unknown. The mechanism of action of the Yuzpe regimen of emergency contraception (ethinyl estradiol 100 mcg and 0.5 mg LNG, two doses 12 h apart [4–6], is also incompletely understood but there is good evidence that it delays or inhibits ovulation in at least some cycles [5]. In the WHO study, the efficacy of both LNG and the Yuzpe regimen decreased with time after intercourse [7] and both regimens had a similar effect on the timing of the subsequent menses, suggesting that the mechanism of action of the two regimens may be similar. It has also been shown that large amounts of synthetic progestogens abolish the mid-cycle lutenizing hormone (LH) surge leading to anovulation and delaying the onset of the subsequent menses [8–11].

To test the hypothesis that it acts as a post-coital agent by abolishing the pre-ovulatory LH surge and by delaying ovulation, we administered LNG 0.75 mg twice to 12 healthy female volunteers in the fertile period (immediately before ovulation) of the menstrual cycle and investigated the effects on the timing of ovulation and of the next menses, bleeding patterns; ovarian activity, and LH concentrations.

## 2. Materials and methods

This was a prospective, randomized, double-blind, cross-over study undertaken in one center. Twelve healthy women (mean age 33.3; range 26–41 years) with regular cycles (mean 27.6 days; range 25–30 days) and mean BMI 25.7 (range 20–34) were recruited. They were all using a reliable non-hormonal method of contraception or were abstinent

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during the study. All subjects gave written informed consent for participation in the study, which was approved by the Lothian Research Ethics Committee.

A method was sought to provide a convenient means of identifying the fertile period prior to ovulation, and thereby to time the administration of LNG. Unipath (Bedford, UK) had developed a technology that can be used in the home to monitor changes in urinary hormones [12]. This monitoring system comprises disposable test sticks and a hand-held monitor, which together are used to detect changes in the levels of oestrone-3-glucuronide (E3G), a urinary metabolite of oestradiol, and LH to indicate the potentially fertile days leading up to ovulation.

The monitor optically measures the intensity of the lines that form on the test sticks after sampling, and the system will delineate three levels of fertility (Low, High, and Peak Fertility) according to the optical signal changes detected. Low Fertility will be displayed from day 1 of the cycle until the hormone levels rise above the baseline levels. A change from Low to High Fertility is triggered by detection of elevated E3G levels, to concentrations typically between 20 and 30 ng/mL. The change from High to Peak Fertility is triggered by the detection of an LH surge, typically with a concentration higher than 30 IU/L. Peak fertility is displayed on the day of the LH surge and on the following day.

Each woman was studied during four cycles and was issued a monitor at the beginning of the study. Subjects were asked to use the monitor according to instructions, and familiarized themselves with the monitors by using it during a pre-study cycle to identify the days of high fertility and the day of the LH surge. They also recorded days of vaginal bleeding.

Data from the pre-study cycle was used to predict the timing of the LH surge and of the fertile phase during the study cycles and thereby to predict when treatment should be administered. The three study cycles followed immediately after the pre-study cycle. Six subjects were randomly assigned to treatment arm A and received LNG in the first study cycle and placebo in the third study cycle. The remaining six subjects were randomized to treatment arm B and received placebo in the first study cycle and LNG in the third study cycle. The second study cycle was a washout phase for all women during which time they also received placebo tablets.

The randomization list was produced using SPSS Rv.Bernouilli function such that each study number was randomly assigned to either treatment arm A or treatment arm B with the same probability, i.e. 0.5.

LNG and placebo were visually identical and were prepacked. Each subject collected a sample of early morning urine daily from the first day of the first study cycle until and including the first day of the menstrual bleed signaling the end of the last study cycle. Samples were frozen and later assayed in batches (with all samples from one subject assayed in a single batch) for measurement of urinary LH, E3G, and pregnanediol-3-glucuronide (P3G).

Quantitative assessment of urinary LH was performed using an LH MAIAclone kit (BIOSTAT-DIAGNOSTICS, Stockport, Cheshire, UK). This method incorporates two high-affinity monoclonal antibodies into an immunoradiometric assay system and offers a working range of 1.5–200 mIU/mL. Urinary P3G was measured using a direct enzyme immunoassay (working range 0.25–32 mmol/L), while direct immunoassay was used to measure E3G levels (working range 8.36–2140 nmol/L. Intra-assay coefficients of variation were 6% for E3G, 10% for P3Gl, and 3% for LH [13]. Geometric means of daily replicates were divided by the respective daily creatinine concentration to correct for variations in the dilution of the urine specimen.

During study cycles 1 and 2, women were asked to take the study medication on the first day of High Fertility as identified by the monitor. However, by the third study cycle, the variation in the number of high fertile days (range 0–8 days) meant that the monitor could not be used to administer medication on LH-2 in every cycle. Therefore, we had to adopt a different method of calculating the anticipated day of the LH peak for each cycle based on the monitor information from the previous cycles (including the pre-study cycle). Hence, in the third study cycle, the medication was taken 2 days prior to the anticipated day of the LH peak. In all cycles the first tablet was taken at 1100 h and the second at 2300 h. A sample of venous blood was collected 5–7 days after treatment, stored and later assayed for progesterone using Coat-A-Cont solid-phase radioimmunoassay. The subjects kept a daily record of all vaginal bleeding experienced during the four cycles, the fertility status information displayed each day on the monitor LCD and the days on which the study medications were taken.

### 2.1. Statistical analysis

We calculated that a total of six subjects in each of the two treatment arms would give more than 90% power to detect a delay of menses of >5 days in 95% of cycles.

Preliminary analysis was performed to determine whether parametric tests were appropriate for analysis of the data. Outlying data points were investigated while the treatment was still blinded. The period effect and interaction between treatment and period effect were tested (two-sample $t$ test) before progressing to testing of a treatment effect and was non-significant. Comparisons between LNG versus placebo cycles was tested by paired $t$ test.

For the purpose of the study the following definitions based on the quantitative data were created.

A significant delay in the onset of next menses: Delay of 5 or more days from the expected onset of menses (based on the mean cycle length for the 2 placebo cycles).

The LH peak was defined as a significant rise in urinary LH concentration, with a minimum of 50% rise above the average baseline level for 4 preceding days and which remained elevated for a minimum of 3 days.

The first day of the LH peak was defined as the day of the

Table 1
Timing of LH peak, predicted day of the LH peak and timing of LNG in treatment cycles for all subjects

| Subjects | Day of the LH peak (LH > 50%) | | | | Predicted day of the LH peak in the treatment cycle | Timing of LNG in relation to the day of LH peak in the treatment cycle | Timing of LNG in relation to the predicted day of the LH peak |
|---|---|---|---|---|---|---|---|
| | Pre-study cycle | Placebo | Placebo (washout) | Treatment | | | |
| S101 | 12 | 13 | 9 | 10 | 11 | −1 | −2 |
| S102 | M | 20 | 19 | 21 | 19.5 | −1 | +0.5 |
| S103 | 12 | 27[c] | 9 | 11 | 9 | −1 | +1 |
| S104 | M | 11 | 12 | 12 | 11.5 | 0 | +0.5 |
| S107 | 17 | 14 | 14 | 13 | 14 | −1 | −2 |
| S111 | 12 | 11 | 15 | 12 | 13 | −1 | −4 |
| S112 | 11 | 11 | 12 | 13 | 11.5 | −5 | −3.5 |
| S105[a] | 14 | 13 | 15 | 14 | 14 | −2 | −2 |
| S106[b] | 14 | 14 | 12 | 23 | 13 | −11 | −2 |
| S108[b] | 17 | 18 | 18 | 25 | 14 | −13 | −2 |
| S109[b] | 14 | 10 | 10 | 38 | 10 | −31 | −3 |
| S110[b] | 18 | 18 | ff | 40 | 18 | −25 | −3 |

[a]The woman with normal LH peak but no significant rise in pregnanediol in the luteal phase = anovulatory cycle.
[b]Women who had a delay of the LH peak by >5 days.
[c]Excluded, unusually delayed ovulation.
ff = excluded, no daily urine available.
M = LH peak not detected by the monitor.

first significant rise (>50% above the baseline) seen at the beginning of the LH peak.

Retrospectively predicted first day of the LH peak for the treatment cycles was the calculated mean of the first day of LH peak in the two placebo cycles.

A significant delay in the first day of the LH peak: Delay of 5 or more days from the expected first day of the LH peak in the treatment cycle (based on the mean first day of the LH peak during the 2 placebo cycles).

Luteal phase: time from the day after the first day of the urinary LH peak (LH+1) until, and including, the day before the first day of the next menses.

Follicular phase: time from the first day of the menses until the day of the first significant rise in urinary LH (LH+0) inclusive.

## 3. Results

A total of 48 menstrual cycles were studied—12 pre-study cycles and 36 study cycles. Data from daily urine samples were available for 34 out of the 36 study cycles. In one woman (S103) the first study cycle, which was a placebo cycle, was prolonged (41 days) as a consequence of a delay in ovulation. Her usual cycle length was 25 days, this cycle was excluded from the analysis. In a second woman (S110) there were no daily urine samples available from the washout cycle as she was abroad on holiday. Therefore, daily urine samples were only available for this subject from two study cycles (the treatment cycle and one placebo cycle).

### 3.1. Timing of administration of LNG

Six women took LNG in the first study cycle and six took it during the third study cycle. During the first study cycle, 10 women took the tablet (either placebo or LNG) on the first day of High Fertility as indicated by the monitor. The remaining 2 women took the tablet on the first day of the urinary LH peak because the monitor failed to identify any high fertile days prior to the LH surge.

The variation in the number of High Fertile days (0–8 days) declared by the monitor meant that the system could not be used to predict LH-2 in every cycle. Therefore, for cycle 3 we calculated the anticipated first day of the urinary LH peak from the information gathered from the pre-study cycle and study cycles 1 and 2 for each woman and instructed subjects to take the tablet 2 days before the anticipated day of the LH peak.

After completion of the study, we retrospectively calculated the predicted first day of the urinary LH peak for every treatment cycle based on the mean first day of the LH peak in the two placebo cycles. When we applied this retrospectively predicted definition to all 12 treatment cycles, the day of taking LNG ranged from 4 days before until 1 day after the first day of the anticipated LH peak. However, in reality, LNG was never taken after the first significant rise in urinary LH concentrations in any treatment cycle. The timing of the LH peak in each of the four cycles, the predicted day of the LH peak day and the timing of LNG and placebo treatment in relation to the start of the actual LH peak are shown in Table 1.

Table 2
Mean length of placebo and treatment cycles

| Mean cycle length | Treatment cycles | Placebo cycles |
|---|---|---|
| All cycles, n = 12[a] | 32.17 (SD ± 3.36) | 26.33 (SD ± .42) |
| N = 4, Delay of >5 days[b] | 42.75 (SD ± 8.42) | 27.13 (SD ± 1.84) |
| N = 8, remaining cycles[c] | 24.88 (SD ± 2.1) | 26.13 (SD ± 1.69) |

[a] p = 0.14.
[b] p = 0.04.
[c] p = 0.12.

### 3.2. Cycle length

Treatment with LNG in the pre-ovulatory period significantly prolonged by 5 days or more the mean cycle length in four women (33% of the sample, Table 2). All 4 women reported vaginal spotting 2 to 3 days after taking LNG and they all had a second episode of vaginal bleeding between 9 and 16 days after the delayed LH peak. In the remaining eight women, there was no significant difference in cycle length between treatment and placebo cycles. One of this group of women, however, reported light vaginal bleeding starting a week after taking LNG, the bleeding continued until she started what she regarded as a normal menstrual period which followed a fall in urinary pregnanediol levels. Her hormone profile during the treatment cycle followed a normal pattern.

### 3.3. The first day of the LH peak

In the four women with long cycles, LNG appeared to abort the LH peak and a subsequent LH peak occurred 7 to 16 days later, followed by a normal rise in urinary pregnanediol. The urinary hormone profile of one woman (S110) is illustrated in Fig. 1. In the remaining eight women, LNG did not affect the timing of the LH peak when taken immediately before ovulation. Fig. 2b illustrates the hormone profile in one of these women (S101).

### 3.4. Length of the luteal phase

In all 12 volunteers the luteal phase was significantly shortened following treatment with LNG as compared with the placebo cycles (mean length 11.5 days [SD ± 1.8] vs. 12.9 days [SD ± 2.5] p = 0.005, Table 3).

### 3.5. The effect on total LH during the luteal phase

Daily urinary LH concentrations were summated from the first day of the LH peak (LH+0) up to the day before the first day of the next menses to give a value for total LH concentrations. The 8 women in whom pre-ovulatory LNG did not affect the cycle length, showed a significant (p = 0.01) decrease in total LH in the treatment cycles (18.7 U/mmoL,

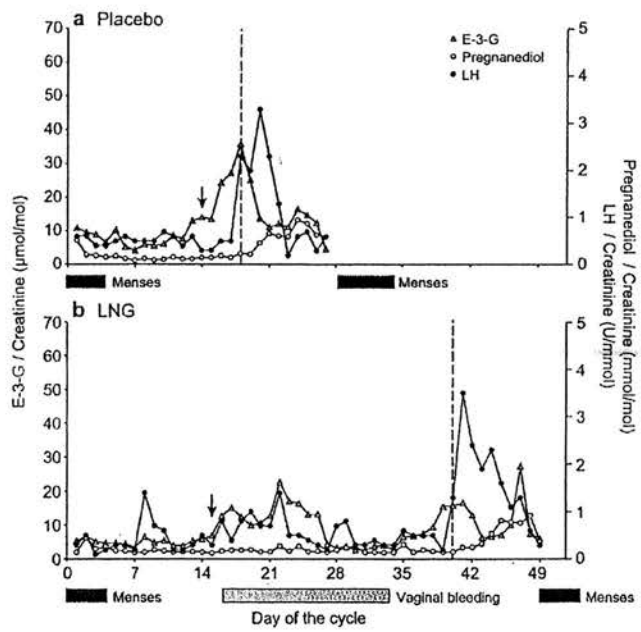


Fig. 1. Daily levels of LH (●) oestrone-3-glucuronide (E3G) (△), and pregnanediol (○), in urine relative to the cycle day. (a) Placebo cycle of a woman (S110) (b) Treatment cycle of the same woman (S110) showing significantly prolonged cycle following pre-ovulatory LNG. ↓, Day of taking LNG or placebo tablet; – – – –, day of the LH surge

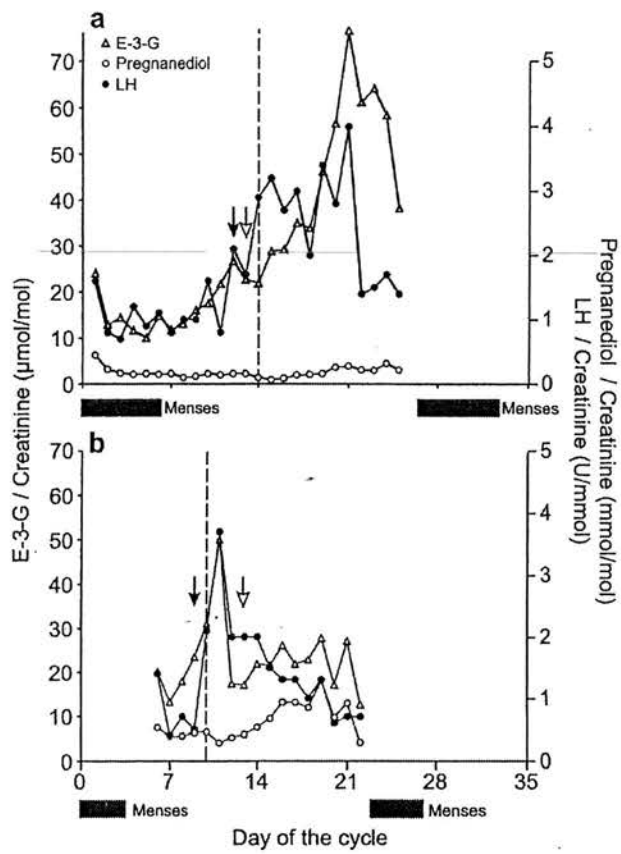


Fig. 2. Daily levels of LH (●), oestrone-3-glucuronide (E3G) (△), and pregnanediol (○), in urine during the treatment cycles. (a) Of the woman (S105) with no significant rise in pregnanediol following LNG. (b) Of a women (S101) with apparently normal cycle length. ↓, Day of taking LNG; ⇓, day of the LH surge in the placebo cycle; - - - -, day of the LH surge.

SD ± 8.9) as compared with the placebo cycles (27.1 U/mmoL, SD ± 13.6). In contrast, among the 4 women with significantly longer cycles after taking LNG, there was no difference in the total LH secretion in the luteal phase (mean total LH = 18.8 mIU/mL, SD ± 8.3; versus mean total LH for placebo cycles of 17.8 U/mmoL, SD ± 2.8; p = 0.81).

### *3.6. Effect on pregnanediol in the luteal phase*

The sum of daily pregnanediol concentrations in the luteal phase (from LH+1 onwards up to the day before the first day of next menses) was compared during the treatment and placebo cycles was employed to indirectly assess the function of the corpus luteum.

In one woman (S105) after taking LNG, there was no significant rise in urinary pregnanediol levels (>0.5 mmol/mol creatinine as expected in the mid-luteal phase) despite an apparently normal LH peak. The mid-luteal serum progesterone level during this treatment cycle was consistent with an anovulation (<5 nmol/L) (Fig. 2a). In the remaining 11 subjects, the total values of pregnanediol did not show a significant difference between placebo or treatment cycles.

## 4. Discussion

Evaluation of daily hormone concentrations confirmed that all 12 women in our study took LNG before the LH peak, and presumably ovulation. Seven women had apparently normal ovulatory cycles after taking LNG. Five of them took LNG on the day before the LH surge and one on the day of the surge. It is possible that the timing of LNG in these women was "too late" to influence an event already well underway. However, in the four women in whom the LH peak and ovulation was delayed, the LNG was taken within 3 days of the predicted LH peak. One woman did not ovulate at all despite having an LH surge 2 days after taking LNG.

Table 3
Length of the luteal phase (n = 12)

| Patient | Treatment cycle | Mean for placebo cycles |
|---|---|---|
| 101 | 12 | 13.5 |
| 102 | 8 | 8.5 |
| 103 | 14 | 14 |
| 104 | 13 | 15.5 |
| 107 | 13 | 14 |
| 111 | 12 | 13.5 |
| 112 | 10 | 14 |
| 105 | 11[b] | 13.5 |
| 106[a] | 12 | 12 |
| 108[a] | 10 | 11.5 |
| 109[a] | 13 | 16.5 |
| 110[a] | 9 | 9 |

[a]Women who had a delay of the LH peak by >5 days
[b]The time from the LH surge to the next menses in the woman with an anovulatory cycle, but a normal LH peak after LNG (Fig 2a)

It is apparent that different women respond differently to the administration of LNG. The effects observed may be related to administering LNG at a specific stage in follicular development. Even though the timing of the LNG in relationship to the onset of the LH surge did not appear to be different between women in whom ovulation was affected and those in whom it was not, it would be naïve to accept that our predicted day of the LH peak based on information gathered in two cycles was always accurate. A more detailed study employing daily serum levels of gonadotrophins and steroid hormones and ultrasound scans to correlate follicular size and maturity to the timing of the administration of LNG might provide an explanation.

The 7 women, who apparently ovulated normally, had a reduced total luteal LH and a shortened luteal phase. Basal levels of LH are essential for the normal secretory function of the corpus luteum [14]. In the mid-luteal phase, LH inhibition by the administration of GnRH antagonists consistently results in luteolysis in women as well as in non-human primates [15–17]. There are no direct ways of measuring whether the function of the corpus luteum is compatible with the establishment of pregnancy. Although there was no significant difference in the urinary pregnanediol levels after LNG, it is possible that the shortened luteal phase observed was a consequence of reduced total LH and may have a contragestive effect.

If LNG acts as an emergency contraceptive only by interfering with ovulation, the expected efficacy should fall below 42% (5 of 12 women). Ho and colleagues [1] reported that LNG reduced approximately 60% of the expected number of pregnancies (estimates were based on the table of probabilities of pregnancy at different cycle days by Dixon et al. [18]). LNG fared better in the WHO study [2] with overall 85% reduction of expected number of pregnancies (the analysis of the prevented fraction was based on the modified Wilcox estimates of conception probabilities [19]).

Both studies reported effectiveness against estimates based on historical data. The fertile period was determined on the assumption that ovulation occurred 14 days before the next expected menses. The validity of using these estimates directly relies on the accuracy of reported menstrual cycle data. Women do not regularly keep records of their menses, and by and large the sexual intercourse responsible for requesting emergency contraception is unpremeditated. Reporting errors are common and the estimates can be inaccurate. In addition, other factors such as biologic variability of the day of the ovulation and the length of the luteal phase, factors affecting the probability of pregnancy unrelated to the timing of intercourse, and heterogeneity among couples in fecundability can distort the estimated number of pregnancies. In a study comparing the efficacy of the Yuzpe regimen of EC with a single dose of mifepristone [20], there were frequent discrepancies among subjects between the stage of the cycle as estimated from the date of the LMP and that suggested by circulating concentrations of progesterone. There has never been a placebo-controlled trial of EC. Thus, it is possible that the genuine effectiveness of LNG as an emergency contraceptive is less than 42%.

One woman (S103) in our study showed a delayed LH peak (on day 27) during a placebo cycle and subsequently the length of that cycle was prolonged to 41 days (her usual cycle length was 25 days). In contrast to the four women who experienced similar prolongation of the cycles after taking LNG, this woman did not report any intermenstrual vaginal bleeding. Although we excluded this cycle from our analysis, similar spontaneously occurring prolonged cycles (with delayed ovulation), can influence the results of studies into emergency contraception.

The discrepancy noted in the estimated effectiveness of LNG and the prevalence of ovulation delay or inhibition in our study may be due to mechanisms of action other than interference with ovulation. Our study was not designed to investigate the other possible mechanisms by which LNG works. However, one woman in our study reported slight vaginal bleeding after taking LNG with an apparently normal LH peak, cycle length and hormone profile. This may suggest an additional effect of LNG on the endometrium [21–24]. Nevertheless, the question remains as to whether similar alterations occur in the endometrium after taking the emergency contraceptive regimen of LNG, and whether these changes are sufficient to prevent implantation and account for the observed contraceptive efficacy of LNG. The effect of progestogens on cervical mucus and on the cervix is well documented and this is thought to be the main mechanism by which the progestogen-only pill exerts its antifertility action [25–27]. However, even if LNG has an effect on cervical mucus, which interferes with sperm penetration, that action is unlikely to prevent pregnancy when taken some 12–72 h after coitus.

The reason for using the monitor to time the administration of LNG or placebo was to avoid having to subject the volunteers to regular blood samples and ultrasound scans.

However, due to the variability in the number of high

fertile days declared prior to the LH surge, greater reliance had to be placed on calendar calculations to predict the LH surge.

In conclusion, we suggest that LNG taken immediately before ovulation acts as an emergency contraceptive by delaying or preventing ovulation. Other plausible actions of LNG including the retardation of the endometrium, interfering with sperm motility and altering cervical mucus may be important, and need to be explored further.

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ELSEVIER

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# Estimating the efficacy of emergency contraception—how reliable are the data?

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**Abstract**

Ninety-four women attending a family planning clinic for emergency contraception (EC) were asked how certain they were of the date of their last menstrual period (LMP), of the timing of intercourse, and how many times in the cycle they had had sex. Urinary pregnanediol concentrations were analyzed in 64 women to assess whether they had ovulated before they used EC. Forty-five women were certain of the date of the LMP, the rest were not. Only four women could not accurately recall the timing of intercourse, and 60% had had intercourse more than once in the cycle. Twenty-one women had urinary pregnanediol concentrations that were inconsistent with their cycle day. Calculations of the efficacy of EC depend on knowing the timing of intercourse in relation to the estimated day of ovulation. The results of this study suggest that these calculations are likely to be inaccurate for a significant minority of women. 

*Keywords:* Emergency contraception; Cycle; Efficacy

## 1. Introduction

Emergency contraception (EC) is widely regarded as a possible solution to reducing the rate of unwanted pregnancies [1]. There has never been a placebo-controlled trial of any method of emergency contraception, and its true efficacy is unknown [2,3]. In recent years it has become accepted practice to express the efficacy of EC as the proportion of expected pregnancies that it appears to prevent [4]. This figure is arrived at by multiplying the number of women who had intercourse on each cycle day by an estimate of the probability of conception for that day and then summing over all cycle days. The probability of conception for each cycle day is commonly calculated from data collected prospectively from couples actively trying to conceive [5]. In these prospective studies, the day of intercourse (from diaries) and the day of ovulation (from biochemical data) are known precisely. In contrast, studies used to calculate the efficacy of EC rely on the subject's recall of the date of the first day of the last menstrual period, and the day of ovulation is calculated from what she says is the usual length of her cycle; biochemical data are not usually collected. Thus, the risk of conception on the day when intercourse occurred and, therefore, the efficacy of EC is estimated from data dependent usually on recall.

In a trial comparing two regimens of EC [6] in which urinary pregnanediol or plasma progesterone were measured on the day of treatment, discrepancies between the time of the cycle suggested by the calendar day and that suggested by biochemical measurement were common. In a similar study undertaken in Spain [7], only 51% of 99 women thought (from the date of the LMP and usual cycle length) to be in the fertile phase of the cycle had hormone levels which were compatible with the fertile phase.

In a small study designed to further explore possible discrepancies (and therefore inaccuracies) in data used for calculations of efficacy, we asked 94 women who had presented for EC how certain they were of the date of their last menstrual period and of the timing of intercourse, and correlated this information with pregnanediol:creatinine ratios in a single urine sample taken on the day of treatment.

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## 2. Materials and methods

Women who had presented to a large family planning clinic for emergency contraception and who were not currently using hormonal contraception were invited to take part in the study but not until after they had received hormonal EC. They completed a brief self-administered questionnaire that asked how confident they were of the date of their last menstrual period and of the timing of the act of intercourse for which they had sought EC. They were also asked how many times in that cycle intercourse had occurred. A specimen of urine was collected and stored at −4°C until samples were later assayed in a single batch for urinary estrone:creatinine and pregnanediol:creatinine ratios (for detail of methodology see Yong et al. [8]). The study was approved by the local research ethics committee and all subjects gave written informed consent.

## 3. Results

Ninety-four women participated in the study and completed the questionnaire. All had presented for EC within 72 h of intercourse. All were less than 42 years of age, and 53% were under the age of 25 years.

### *3.1. Date of LMP*

Asked about the certainty of the date of the last menstrual period 45 (48%) women reported that they were "absolutely certain," and 19 (20%) of these women kept a diary. Twenty-two (23%) women felt "fairly sure" of the date of their LMP (to within plus or minus 1 day). Twelve women (13%) could only estimate their LMP to within plus or minus 3 days, and 9 (10%) could only estimate it to within 1 week either side of the possible date. Six women said they had "no idea" of the date.

### *3.2. Timing of intercourse*

Fifty-two percent of women were sure of the time that intercourse had occurred to within 30 min, and 85% were sure to within 1 h. Only four women stated that they could only be certain of the timing of intercourse to within 9–12 h.

### *3.3. Other episodes of intercourse*

Thirty-seven (40%) women said that they had not had any other episodes of intercourse that cycle. Forty (43%) said they were definitely not at risk of conception despite further acts of intercourse because they were also using barrier or hormonal methods of contraception (29 and 11 women, respectively) in that cycle. Seven more women regarded themselves not to be at risk, however they only stated that they "usually used" barrier methods, not that they had used one in that particular cycle. Six women admitted to being at risk of pregnancy because of other episodes of unprotected intercourse that cycle. Half of these women said it had been on only one other occasion, and half admitted that it had been on several occasions. One woman declined to answer the question. In the clinical consultation before the provision of EC, none of these 57 women admitted to other episodes of unprotected intercourse.

### *3.4. Time of cycle*

Twelve of the 94 women declined to provide a urine specimen and were therefore excluded from the analysis relating biochemical data to calendar-calculated cycle day. Eighty-two women completed both parts of the study; however, the laboratory was unable to locate the results of the urinary assays of four women. A further 14 women were excluded from the biochemical analysis: 11 were using a hormonal method of contraception or had done so within the last 3 months, two had irregular menstrual cycles, and one had been unable to give the date of her LMP when asked in the clinic (Figure 1). A total of 64 women were, therefore, entered into an analysis comparing time of cycle according to calendar with that estimated from urine estrone and pregnanediol values.

Fifty-six women (87.5%) were recorded as having a usual cycle length of 28 days, six had an usual cycle lasting between 30 and 35 days in length. Twenty-three women (36%) had had intercourse during the fertile period, defined as 3 days before to 2 days after the estimated day of ovulation. Two investigators independently reviewed the results of urinary steroid concentrations. A urinary pregnanediol:creatinine ratio of ≥0.5 was taken to indicate ovulation. Twenty-four women (41%) presented in the follicular phase of the cycle (between 11 days and 1 day before the day of ovulation predicted on the basis of LMP and normal cycle length). Two of these had urinary steroid concentrations that clearly indicated that they had already ovulated. Eight women presented on the day of ovulation as estimated by the calendar; according to the biochemical data, three of these women had clearly already ovulated (two had pregnanediol levels of 0.7 and one of 1.0). Thirty-two women presented in the luteal phase according to the date of LMP, and 28 of these presented on day +1 after ovulation or later but before day +11 (after which time pregnanediol:creatinine values would be expected to fall to <0.5). Fourteen of the 28 women had not ovulated according to urinary pregnanediol concentrations.

We did not arrange to follow-up these women after they had used EC; however, three of them returned to the clinic having conceived. One kept a diary and was absolutely certain of the date of her last menstrual period. She was also certain of the time when intercourse occurred and adamant that she had had intercourse only once in that cycle. According to her dates, she had intercourse on day 16 and presented for EC on day 18 of a cycle that usually lasted 28

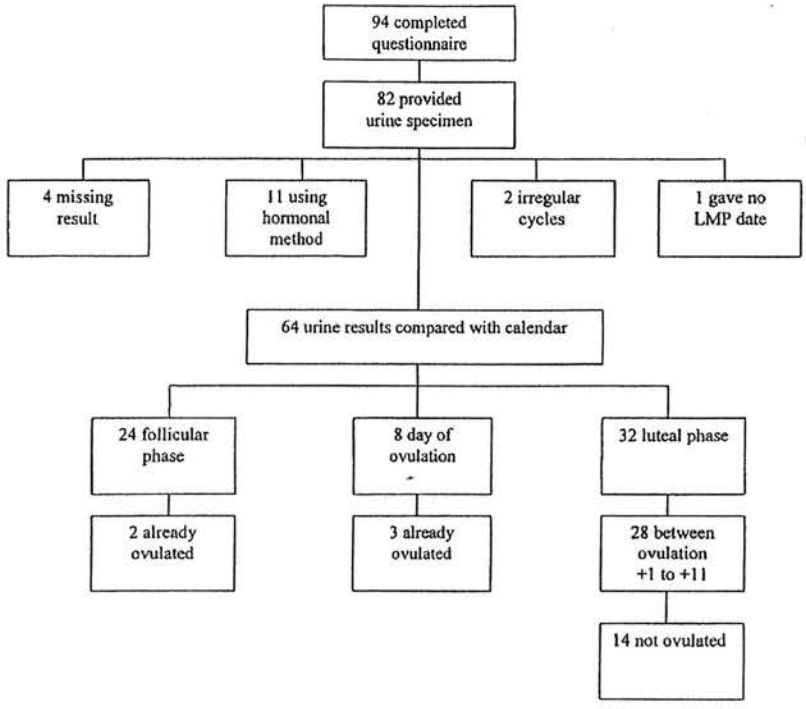


Fig. 1. Progress through the study of the 94 women who attended for emergency contraception.

days. Using Wilcox's data for calculating the risk of conception, this woman would have been estimated to have been at no risk since she presented for treatment four days after the usual day of ovulation. On day 18, her urinary estrogen:creatinine ratio was 26.5 and pregnanediol:creatinine ratio 0.16, suggesting that she had not yet ovulated but that a mature follicle was present. Case two was also sure of her dates although she did not keep a diary. Her usual cycle length was 28 days, she had had unprotected intercourse on day 14 and presented for treatment on day 15. According to Wilcox and colleagues [5], the risk of conception would have been around 30% if intercourse occurred on the day of ovulation and no more than 12% if it occurred on the day after ovulation. Urinary estrogen:creatinine value was 8.9 and pregnanediol 0.3 on day 15, values not suggestive of imminent ovulation. This woman had had one act of intercourse earlier in the cycle for which a condom was used. It is likely that she had further episodes of intercourse after taking EC and conceived as a result of one of these episodes but we have no way of verifying this. The third case was a woman with a 28-day cycle with no idea of the date of her LMP but who guessed she might have had intercourse on day 12. She presented for EC on day 15 when urinary estrogen:creatinine measured at 14.1 and pregnanediol:creatinine 0.22. She came back again on Day 22 of the cycle (based on her earlier guess) having had intercourse 3 days earlier on Day 19. All three women had their pregnancies terminated.

## 4. Discussion

This was a small pilot study designed specifically to determine how certain women were of the date of their last menstrual period and whether the degree of certainty correlated with the day of the cycle estimated by the calendar and the prevailing pattern of hormone secretion. Only 20% of women presenting for EC kept a written record of the date of menses, but more than 30% of them had biochemical findings that appeared to be incompatible with their cycle day as estimated by the calendar. Among those women who did not keep a diary, the greater the degree of uncertainty about the date the higher percentage of inconsistent results ["very sure," 15.3% inconsistent; "fairly sure" (±1 day), 27.2% inconsistent; "quite sure" (±1–3 days), 41.6% inconsistent].

There are four possible reasons for these inconsistencies: the date of the LMP was incorrectly recalled; the cycle was an anovulatory cycle; the usual cycle length was incorrect; or the cycle in which the woman sought EC was of atypical length. More than half of the women participating in the study admitted to a degree of uncertainty about the date of

their LMP when asked directly. As in our previous study [6], the biochemical data were more likely to be incompatible with the calendar day of the cycle among women presenting in the luteal phase when their LMP was a more distant memory. Eighty percent of women taking part in the study did not record their period dates in a diary, and it is very possible that many of those who did not record the date were wrong by a day or two. Whatever the reason for it, this degree of inaccuracy could mean a difference in the estimated risk of pregnancy of between 30% on the day of ovulation, 12% 1 day later, and no chance of conception 2 days after ovulation [5]. Discrepancies of this magnitude will significantly alter the estimated number of pregnancies that would be expected to occur among a cohort of women using EC and, therefore, will also have a significant impact on the calculated efficacy of the method.

It is possible that women are not being honest about the date of their last menstrual period or about the number of times they had intercourse during the cycle and whether or not they had used a condom. They may feel that fewer questions will be asked and EC more willingly provided if they claim some certainty about the date of their LMP and only one episode of intercourse. But we purposely administered the questionnaire after they had been given EC.

Over 90% of subjects said they usually had a 28-day cycle. That is the average cycle length and most women are likely to regard themselves as being average. Unless they are actively trying to conceive or using natural family planning methods, it seems plausible that most women hazard a guess at the usual length of their menstrual cycle. Even if they do know, cycle length varies by a day or two from month to month. In a study of over 650 women with regular cycles, while the median cycle length was 28 days, only 12.4% of cycles were actually 28 days in length [9].

Could the high rate of discrepancies that we identified among women presenting in the luteal phase be because of frequent anovulatory cycles? In a longitudinal study of patterns of menstruation, Metcalf and MacKenzie [10] demonstrated ovulation occurring in 62% of women aged 20–24 years, 88% of women aged 25–29 years, and 91% of women aged 30–39 years. In our study, we would need to hypothesize a rate of anovulatory cycles of 50% which seems unlikely.

Calculations of the efficacy of EC assume that every user (and her partner) is fertile; that each cycle is ovulatory; that the calculated day of ovulation is accurate; that intercourse occurred only once in that cycle; and that pregnancy, if it occurs, is the result of the act of intercourse for which EC was provided. In a recent re-analysis [11] of the data on which the Wilcox [5] estimates of the risk of conception are based, the authors cast serious doubt on the reliability of using the calendar day of the cycle alone to calculate the risk of pregnancy. It has now been demonstrated in three studies of women using EC (the present one, and those described by Glasier and colleagues [6] and Espinos and coworkers [7]), that the calculated day of ovulation is often incorrect. Moreover, our data demonstrate that despite what women say when requesting EC, an earlier act of unprotected intercourse is not uncommon. It is also clear from other studies [12] that women often have unprotected intercourse after using EC and that this accounts for some of the pregnancies attributed to EC failure. Providers often seem surprised, and users somehow cheated, when pregnancy occurs after emergency contraception has been used. It is impossible now—for obvious ethical and practical reasons—to undertake a placebo-controlled trail of the efficacy of EC. While we cannot think of a superior method of calculating efficacy than the one which is being widely used, we feel that authors who write papers on the efficacy of a method of EC should acknowledge the shortcomings of the calculations used.

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# Safety of Emergency Contraception

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**Emergency contraception (EC) prevents pregnancy. Four regimens are available in different parts of the world, a combination of ethinyl estradiol and levonorgestrel, levonorgestrel alone, mifepristone, and emergency insertion of an intrauterine device. All the regimens are also used either as long-term contraception or, in the case of mifepristone, as an abortifacient, and considerable data indicate their safety when used in these ways. Data on safety when the regimens are used as EC are lacking, but theoretically, and from practical experience, all appear to be extremely safe, particularly when compared to the risks of pregnancy. There has been a tendency to over-"medicalize" EC. Prescribing EC is simple. Consideration should be given to making EC available off prescription because it is so safe.**

Emergency contraception (EC) prevents pregnancy. It has been calculated that the use of EC after unprotected intercourse will prevent some 75% of pregnancies.[1] Many countries have no licensed preparation for EC, although probably every country has access to a standard method of contraception that can be used in the emergency, postcoital situation. There are very few data on the safety of licensed EC preparations. Much of what can be said about the safety of EC stems from clinical experience and common sense.

This paper will concentrate on four compounds or devices shown to be effective in preventing pregnancy after intercourse. Two of these—the combined estrogen-progestin (Yuzpe) regimen and levonorgestrel alone—are licensed and marketed as EC in some countries. Mifepristone (RU 486) is licensed for induction of abortion in four countries (France, Sweden, United Kingdom, and China) and used for EC in China only. The intrauterine device (IUD), widely available as a regular method of contraception, is used postcoitally under certain circumstances in a few countries.

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### The Combined Estrogen-Progestin Regimen

The estrogen-progestin regimen has been widely used in Europe since the mid-1980s; however, very few data on its safety are available. Because this regimen exposes women to the same type of hormones as those in the combined oral contraceptive pill (COC), there has been a tendency to extrapolate from the known risks of these preparations. Long-term use of COCs is associated with an increased risk of both arterial[2] (myocardial infarction and cerebrovascular accident) and venous[3] (deep venous thrombosis and pulmonary embolism) disease. Most studies suggest that the risk of venous thromboembolism (VTE) is dose dependent and is higher with pills containing 50 mcg estrogen than the low-dose (30 to 35 mcg) pills in common use today.[4] While the estrogen-progestin regimen exposes a women to a total of 200 mcg ethinyl estradiol, the exposure is acute. One small study[5] of a high-dose estrogen regimen for EC found a detrimental effect on clotting factors, while a similar study failed to show any consistent effect from the regimen.[6]

The combined estrogen-progestin regimen was licensed in 1984 (as Schering PC4), since then it has been used more than 4 million times. Few adverse events have been reported to the Committee on Safety of Medicines in the United Kingdom.[7] As of July 1996, there were 115 reports of 159 reactions (some women having more than one), 61 of which were pregnancies. Only 3 cases of VTE (one fatal) and 3 cases of cerebrovascular disorder had been reported, and in none was the relationship between the regimen and the event clear cut. Haematologists have reported further cases of VTE at recent meetings in the United Kingdom, but these are anecdotal, and other risk factors such as recent pregnancy or prolonged immobilization are commonly involved. It should be remembered that the reason for taking EC is to prevent pregnancy. All the cardiovascular risks of estrogens are much more common in pregnancy than they are during standard, long-term COC use. The risk of VTE during pregnancy is in the order of 60/100,000 per year and is likely to be considerably less than the risk associated with using EC.

Both the World Health Organization[8] (which added the estrogen-progestin regimen to its essential drugs list in 1996) and the International Planned Parenthood Federation[9] have stated recently that there are no absolute contraindications to the combined estrogen-progestin regimen, except known pregnancy. The regimen will not work if a woman is already pregnant when she uses it. If she inadvertently uses it in the presence of an ongoing pregnancy, it will almost certainly do no harm. Reliable data on the outcome of pregnancy after the regimen has failed are lacking, but the lack of demonstrable teratogenicity of COCs[10, 11] and the timing of the administration of EC (long before organogenesis starts) are reassuring. Thus the combined estrogen-progestin regimen is contraindicated only because it does not work once pregnancy is established, not because it is known to be harmful.

### Levonorgestrel

Although there are few data on the use of levonorgestrel (LNG) for EC, it seems likely to become the method of choice in many countries. The one published randomized controlled trial comparing LNG with the Yuzpe regimen demon-

strated a lower incidence of side effects, particularly nausea and vomiting.[12] Levonorgestrel has been used for many years both alone (in low doses) in the progestogen only pill (POP) and in combination with estrogen in COC preparations. There have been many fewer studies on the safety of long-term use of the POP than of the COC, but the existing data are largely reassuring.[13] Progestins are known to have an adverse effect on serum lipids and triglycerides, biochemical changes that are associated with an increased risk of heart attack and stroke. It is unlikely that these effects would have any clinical relevance in the acute use of LNG as EC. Levonorgestrel has no known adverse effects on clotting mechanisms. Recent data[14] showing an increased risk of breast cancer among long-term POP users are almost certainly not relevant to EC use.

If further studies confirm the equivalent efficacy and superior side effect profile of LNG compared with the Yuzpe regimen, it is likely that LNG will become the preferred compound as the concerns about VTE can be forgotten.

**Mifepristone (RU486)**

Excluding those from China, only two studies of the use of the antiprogesterone mifepristone as EC have been published.[14,15] A larger trial undertaken by the World Health Organization (WHO) is complete but not yet published. Mifepristone has been available as a medical method for pregnancy termination for almost a decade. The dose used for this is usually 200 mg or 600 mg. If mifepristone is to be developed as an EC, it is likely that the dose will be less than 50 mg. Mifepristone for abortion induction is safe and has no known serious side effects. (The few serious adverse events that have been reported have been attributed to the prostaglandin part of the regimen.) Only the antiglucocorticoid effects of antiprogesterones might give theoretical cause for concern, and data for both single use (in abortion) and long-term, usually low-dose, use[16] (as contraception) are very reassuring. The side effect profile of mifepristone as an EC is considerably better than that of the Yuzpe regimen, with a significant reduction in all side effects including nausea and vomiting.

It is likely that if mifepristone or another antiprogesterone becomes widely available for EC, it will be regarded as an extremely safe product without the cardiovascular concerns associated with contraceptive steroids. Indeed, in many parts of China it is now the method of choice.

**The Intrauterine Device**

The IUD is a safe and effective long-acting method of contraception that acquired a somewhat tarnished reputation following reports of increased incidence of pelvic infection and subsequent infertility. Many of the adverse reports related to one particular device, the Dalkon Shield. Recent large reviews of pelvic infection and other aspects of safety have been extremely reassuring.[17,18]

The IUD is a very effective emergency contraceptive usually reserved, at least in the United Kingdom, for women who are beyond the 72-hour limit for oral EC. Insertion is an invasive procedure and can be uncomfortable. If the IUD is inserted using aseptic techniques, the risk of infection is very small. It has been suggested that women in need of EC may often, because of their sexual lifestyles, be at increased risk of pelvic infection. Thus screening for sexually transmitted infection or, if this is not practical, antibiotic prophylaxis using a broad spectrum antibiotic known to be effective against chlamydia is usually recommended before IUD insertion. The risk of uterine perforation at the time of insertion should be no different from that associated with routine IUD use.

Insertion may be associated with pain and syncope. Anecdotally, this is more common with postcoital insertion than with standard use. Women requesting EC are likely to be young and nulliparous and therefore likely to have a small uterus and narrow cervical os. They are also much more likely to be anxious and upset and have little time to be informed, in a reassuring manner, about the IUD.

While pelvic examination is not necessary before oral EC, it is mandatory as part of IUD insertion.

**The Consultation**

The management of women requiring EC is really very straightforward, but because in many countries it must be prescribed by a doctor, there is a tendency to over-"medicalize" the consultation. It should not be forgotten that any woman who has a packet of COC pills has the wherewithal to make her own EC preparation. Indeed, US doctors have recently been advised by the US Food and Drug Administration how to use the COC as an emergency contraceptive.[19]

Physicians have all been taught that it is essential to take a full and detailed medical history before prescribing treatment. Because EC is so safe, this is probably not strictly necessary. If you have access to a choice of methods, then a history of VTE might sensibly indicate a method that does not contain estrogen. If estrogen-progestin is the only regimen available, however, it should be used since the risks of VTE in pregnancy are much greater. The only requirement is to ascertain that the woman is not already pregnant. If a woman is certain of the date of her last menstrual period and there is no clinical suspicion of pregnancy, it is not necessary to do a routine pelvic examination or a pregnancy test.

Above all clinicians need to remind themselves that they are not starting someone on the COC pill. It is not necessary to weigh the woman, do a breast examination, take a cervical smear, undertake urinalysis, or measure serum cholesterol. It cannot be stressed enough that you are prescribing *emergency* contraception. Blood pressure may be elevated because of the stressful nature of the consultation, and it is unlikely that a single abnormal reading would be taken as a contraindication to prescribing EC.

Any medical or gynecological problems that come to light do not necessarily need to be dealt with at the same consultation. It is important to inform the woman about the nature and mode of action of EC (as best we understand it), the possible side effects, the timing of next menses, and what to do in the event of vomiting or delay in the onset of next menses. Safe sex and future contraceptive plans should be discussed, and the woman should be informed that it is perfectly safe and acceptable to use EC again if the need arises. A follow-up appointment is not absolutely necessary, but should be offered as an opportunity

for review, particularly if other issues have been raised during the consultation.

### Who Should Provide Emergency Contraception?

Emergency contraception has to be prescribed by a doctor in many Western countries. In some countries in the Far East and Eastern Europe, LNG EC is available over the counter. Who can prescribe or provide EC depends of the laws of each country. In some countries nurse prescribing may be routine; given that EC is so safe, there are no reasons (other than legal ones) why nurses should not prescribe it. It is arguably much safer than many other drugs, such as paracetamol, which can be bought in supermarkets. Indeed, many have argued that it is safe enough to be available off prescription.[20] For a variety of reasons[7] EC is still not available over the counter in most Western countries, although it may become available if the LNG-only regimen fulfills its promise as an effective method.

### Conclusion

There are very few data on the safety of currently available EC regiments, but both the theoretical and empirical evidence is reassuring, and any risks are substantially lower than those of pregnancy.


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COMMENTARIES

# Emergency contraception: time for de-regulation?

Abortion rates are rising. In 1991 around 200 000 pregnancies were terminated in the United Kingdom. While some of these conceptions result from contraceptive failures, as many as half arise in couples using no contraception at all. In a study of 733 women undergoing pregnancy termination in Oxford (Duncan *et al.* 1990), over 40% admitted that they were using no contraception at the time they conceived. It is argued that more open attitudes towards sexuality and better sex education would improve contraceptive prevalence. Even if this is true it will be many years before such changes have any impact on abortion rates. We should look for other solutions.

In the Oxford study, 528 of the pregnancies might have been predicted as either no contraception was used or a recognisable contraceptive failure occurred. Eighty per cent of these pregnancies might have been prevented by the use of emergency contraception. In the event only 18 women admitted to using it. Emergency post coital contraception (PCC) can prevent pregnancy: it is important, therefore, to consider why it is so seldom used and how its uptake might be increased.

Is post coital contraception effective? The true efficacy of emergency contraception and particularly of the combined oestrogen–progestogen oral contraceptive has recently been questioned (Silvestre *et al.* 1991). Efficacy is difficult to calculate precisely since not all women who use PCC are genuinely at risk of conception. In a recent study of 398 women using the standard combined oestrogen–progestogen regime only four conceived—a failure rate of 1% of the total sample (Glasier *et al.* 1992). Calculating the chance of conception for each individual woman based on the timing of intercourse (Dixon *et al.* 1980), 23 pregnancies would have been anticipated and over 80% were prevented by PCC. It does not really matter how you do the calculations, emergency contraception is clearly effective. The IUCD—used in women in whom combined oestrogen–progestogen is relatively contra-indicated or in those who present beyond 72 h after intercourse—is even more effective: only one pregnancy occurred in 879 post coital insertions and that pregnancy miscarried spontaneously (Fasoli *et al.* 1989).

Most women presenting for PCC are young and have never given birth. IUCD insertion is invasive and the method not usually ideal for continuing contraception. The combined oestrogen–progestogen regimen has its drawbacks, mainly a high incidence of side effects, particularly nausea and vomiting which may interfere with both compliance and efficacy. Prospects for alternative and better methods are promising. It has recently been demonstrated that the antiprogesterone mifepristone (RU486) given as a single dose of 600 mg is a highly effective post coital agent. No conceptions occurred in a total of almost 600 women treated within 72 h of intercourse (Glasier *et al.* 1992; Webb *et al.* 1992). Side effects were significantly less frequent than among women treated with the standard combined oestrogen–progestogen regime.

If emergency contraception works why then don't women use it? In Duncan and colleagues' study (1990), 30% of women did not know about emergency contraception and another 10% did not know where to get it. Similar figures were reported in two other studies (Johnston & Howie 1985; Burton *et al.* 1990). The RCOG Working Party on Unplanned Pregnancy (1991) highlighted the need for better information and public health education about PCC. In a survey commissioned by Schering (1990), over 75% of 1007 women had heard of PCC but only 10% had an accurate knowledge of its time limits. Public advertising campaigns could rapidly increase awareness and knowledge of emergency contraception but would this increase its use?

Licensed in the UK since 1984, oral PCC is available only from a doctor. Because it must be used within 72 h of intercourse, its use constitutes an emergency. It can be difficult to get an emergency appointment with a GP and facing interrogation by reception staff as to the nature of the emergency deters even the most persistent woman. Asking for PCC involves discussing a particular act of intercourse, something which most people, especially the young, find embarrassing—particularly when it is with the doctor who looks after the rest of the family. Community family planning clinics, while more anonymous, are not widespread and in those places where they do exist are often held only once each week. In our experience the greatest need for emergency contraception is at weekends when GP surgeries and family planning clinics are closed. While some hospital casualty departments provide a service (usually involving referral to the on-call gynaecologist) many refuse to do so. In reality, emergency contraception is not easy to obtain even if you do know where and when to get it.

If the use of emergency contraception is to have a significant impact on abortion rates then it must be made more easily available. The time has come to consider the supply in pharmacies of over-the-counter oral post coital contraception. The arguments in favour are outlined above; the arguments against are concerned with safety and the lack of opportunity for follow up. Is the current regimen of PCC dangerous? The only contra-indications are pregnancy and a history of contra-indications to oestrogen, such as thrombo-embolism. While clear warnings of these conditions could be included in the packaging, it

is highly unlikely that any woman, whatever her history, would suffer severe adverse effects from taking 200 μg of ethinyl oestradiol on one occasion. There is no evidence of any change in clotting factors (Webb *et al.* 1992) following the use of the standard regime and pregnancy—whether continued or terminated—for women with contra-indications to oestrogen would be far more hazardous. The vast majority of users would be healthy young women. It is possible that a minority would repeatedly use PCC as a definitive method of contraception. This happens already, but most people motivated enough to use PCC soon find it an inconvenient and disorganised way to arrange their contraceptive needs, and PCC over the counter would not be free. It could be argued that an opportunity to counsel women about a more long term method of contraception at the time of presentation for PCC would be lost. Condoms are widely available from pharmacies and supermarkets but no one would argue that their availability should be limited to clinics where users could be counselled about sexuality. A spokesman for the Family Planning Association recently expressed the opinion that it would be more appropriate to make emergency family planning services more accessible at times women need them (Anon 1992). The two solutions are not mutually exclusive.

Emergency contraception does prevent pregnancy, and if it were easily available and widely used might prevent significant numbers of unwanted pregnancies. Many other drugs potentially far more dangerous are already available over the counter. Pharmacists are highly trained and probably as capable of advising women about the correct use of the drug as a harassed gynaecological houseman who knows little about contraception. It is time for the medical profession and the government to give serious consideration to making oral emergency contraception available over the counter.

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# Teenagers' knowledge of emergency contraception: questionnaire survey in south east Scotland

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Abstract

*Objective*—To determine the level of knowledge of emergency contraception among 14 and 15 year olds.

*Design*—Confidential questionnaire survey.

*Setting*—10 secondary schools in Lothian, south east Scotland.

*Subjects*—1206 pupils predominantly (98.7%) aged 14 and 15 in the fourth year of secondary school.

*Main outcome measures*—Knowledge of the existence of emergency contraception; of its safety, efficacy, and time limits; and of where to obtain it.

*Results*—1121 (93.0%) fourth year pupils aged 14-16 had heard of emergency contraception. 194 girls (32.7%) and 168 boys (27.5%) had experienced sexual intercourse. Of girls who had experienced sexual intercourse, 61 (31.4%) had used emergency contraception. Knowledge of correct time limits was poor, sexually active girls being the most knowledgeable. Pupils attending schools ranked lower than the national average for academic attainment were less likely to have heard of emergency contraception and more likely to have been sexually active. 861 (76.8%) pupils knew they could obtain emergency contraception from their doctor. 925 (82.5%) pupils believed emergency contraception to be effective but 398 (35.5%) thought it more dangerous than the oral contraceptive pill.

*Conclusions*—One third of sexually active girls aged under 16 in Lothian have used emergency contraception. This may help explain the fairly constant teenage pregnancy rates despite increasing sexual activity. Scottish teenagers are well informed about the existence of emergency contraception. However, many do not know when and how to access it properly. Health education initiatives should target teenagers from less academic schools as they are more likely to be sexually active at a young age and are less well informed about emergency contraception.

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## Introduction

In 1989 the rate of conceptions among girls aged under 16 in England and Wales was 9.5 per 1000—the highest in western Europe. In 1991 the government declared its aim to reduce these conceptions by at least 50% by the year 2000.[1] In 1993 the rate in England and Wales had fallen to 8.1 per 1000. Johnson *et al* have reported that age at first intercourse has fallen in Britain over the past four decades.[2] A total of 18.7% of women aged 16-19 interviewed in 1990-1 had been sexually active before the age of 16 as compared with less than 1% of a cohort of women aged 55-59 at the time of interview.

If teenagers have sexual intercourse before the age of 16 they are less likely to use contraception than if first intercourse occurs at a later age.[3] Emergency contraception can prevent pregnancy if unprotected intercourse occurs but potential users must know about it and where to obtain it. Knowledge of emergency contraception has improved over the past decade but previous studies were among adults or teenagers who were already pregnant.[4-6] We report a questionnaire survey of the knowledge of emergency contraception among pupils in 10 secondary schools in south east Scotland.

## Subjects and methods

The survey was done in late 1995 among fourth year pupils in eight state schools and two private schools in the Lothian region of Scotland. The head teachers of 14 out of a total of 47 state secondary schools (all mixed sex and ability) in the region were approached about the survey. Schools were selected by the local education department (which agreed to the study) on the basis that they had participated in little research recently. Six schools refused. All 14 private secondary schools in the region were invited to participate. Eight refused and one failed to reply. The first two private schools to agree to the study (one mixed, one girls only) were enrolled.

The questionnaire was developed with the help of teenagers attending the Edinburgh Brook Advisory Centre and the mode of administration piloted among fourth year pupils attending a secondary school not included in the study.

Seven of the 10 schools sought parental consent for the survey and five pupils were withdrawn. All fourth year pupils at school on the day of the questionnaire took part. Questionnaires were administered by AG and LG under examination conditions without allowing discussion. In order to encourage honest answers the anonymity and confidentiality of the questionnaire were emphasised at the start of each session and pupils put the completed questionnaire in an unmarked envelope before placing it in a collecting box. Pupils who were reluctant to participate were free to spoil the questionnaire, but only two did so. At the end of each session the correct use of emergency contraception was discussed.

## Results

Of the 1206 pupils (612 boys, 594 girls) who completed the questionnaire, 257 (21.3%) were 14 years of age and 933 (77.4%) were aged 15; only 16 (1.3%) were 16 years of age. All were included in the analysis. A total of 1121 (93.0%) pupils had heard of emergency contraception. Girls (584; 98.0%) were more likely to have heard of it than boys (536; 87.0%). A history of sexual activity was not associated with a greater likelihood of having heard of emergency contraception.

Table 1 summarises the results by academic attainment. Pupils attending schools ranked higher than the national average for academic attainment at standard grade (the O level equivalent in Scotland) in the Scottish Office league tables[7] were more likely to have heard of emergency contraception than those attending schools below average for academic attainment.

Girls were more likely than boys to have had sexual intercourse (194 (32.7%) *v* 168 (27.5%)), though 101 (16.5%) boys and 61 (10.1%) girls preferred not to say whether they had been sexually active. Of the 258 pupils aged 14, 29 (22.0%) boys and 33 (26%) girls said they had experienced sexual intercourse. Pupils from less academic schools were more likely to have had sexual

Table 1—*Survey results according to academic attainment of school*

| | Schools above national average† | Schools below national average† | Total |
|---|---|---|---|
| No of questionnaires completed | 613 | 593 | 1206 |
| No of boys | 308 | 304 | 612 |
| No of girls | 305 | 289 | 594 |
| No (%) heard of emergency contraception | 583 (95.1) | 538 (90.7) | 1121 (93.0) |
| No (%) of sexually active girls | 74 (24.3) | 120 (41.5) | 194 (32.7) |
| No (%) of sexually active boys | 66 (21.4) | 102 (33.6) | 168 (27.5) |
| No (%) knowing correct time limit | 176 (28.7) | 142 (23.9) | 318 (26.4) |

† National average is 26% of pupils gaining five or more standard grade examination (O level) passes at grade 1 or 2.

Table 2—*Sources of knowledge about emergency contraception (1121 pupils)*

| Source | No (%) of pupils |
|---|---|
| School | 437 (39.0) |
| Magazines | 425 (37.9) |
| Friend | 253 (22.6) |
| Family member | 197 (17.6) |
| Leaflet or poster | 186 (16.6) |
| General practitioner, family planning clinic, or Brook Advisory Centre | 103 (9.2) |
| TV and radio | 52 (4.6) |
| Cannot recall | 242 (21.6) |

intercourse before the age of 16. Sixty one (31.4%) girls who admitted to sexual intercourse said they had used emergency contraception and 46 boys (27.4%) said their girlfriend had used it.

Knowledge of the correct time limit for emergency contraception (72 hours) was poor and unrelated to the academic standard of the pupil's school. Given a choice of time limits, only 318 (26.4%) pupils gave the correct answer; 271 (22.4%) did not know, 173 (14.3%) thought emergency contraception had to be used within 48 hours after intercourse, and 332 (27.3%) thought it had to be used within 24 hours. Girls who had been sexually active were most likely to know the correct time limit (108; 56.2%). Only 20 (11.9%) sexually active boys gave the correct answer.

Asked where they had learnt about emergency contraception, pupils gave school (437 pupils; 39.0%) and magazines (425; 37.9%) as the commonest sources (table 2). Most pupils (861; 76.8%) knew that emergency contraception was available from general practitioners. Family planning clinics (776 pupils; 69.0%), Brook Advisory Centres (345; 31.0%), and accident and emergency departments (130; 11.6%) were given as other sources.

Three quarters of pupils agreed with the statement, "If a girl under 16 is given emergency contraception by her doctor, the doctor should not tell her parents without her permission." Most pupils (925; 82.5%) believed that emergency contraception would prevent pregnancy on all or nearly all occasions. However, 398 pupils (35.5%) agreed with a statement that using emergency contraception twice a year is more risky to a woman's health than taking the oral contraceptive pill. Only 151 pupils (13.5%) thought it was safer to use emergency contraception twice in one year than to take the pill. When asked about side effects of emergency contraception 91 (8.0%) pupils believed infertility to be a potential risk.

## Discussion

We believe this to be the first survey of the knowledge of emergency contraception among teenagers not seeking contraceptive advice and including both boys and girls. The sample selected was likely to be representative of teenagers in the area, as it included urban and semirural schools with a range of academic attainment. Of the schools refusing to participate, three objected on moral grounds, one gave no reason, and 10 said they were too busy. One other school failed to reply. Though it is possible that schools that particularly prided their sex education programme agreed to participate, we do not think this was so. In seven schools over 80% of pupils were present when the questionnaire was administered and in two over three quarters were present. In one school 45% of the pupils were absent. That school had the lowest level of academic attainment and the highest prevalence of teenage sex. Refusal of schools to participate and absence or truancy among pupils may have contributed to a sample bias.

The proportion of sexually active teenagers was greater in our survey than in the sexual attitudes and lifestyles survey covering England, Wales, and Scotland in 1990-1[2]; 18.7% of girls in that survey as compared with 32.7% in our local survey were sexually active. Interestingly, the figures for boys in the two surveys were similar (26.7% and 27.5%). Our figure for all sexually active teenagers may be an underestimate because of the large proportion (particularly boys) who preferred not to say whether they had been sexually active. Differences between the studies may reflect the different methodologies used. Alternatively more teenagers may now become sexually active at a younger age.

The number of pupils who had heard of emergency contraception was reassuringly higher than in previous studies. George *et al* studied a general practice based population of 1290 women aged 16-50, of whom 78.6% had heard of emergency contraception.[8] Pearson *et al* interviewed 167 pregnant teenagers, of whom 81% had heard of it.[9] In our study knowledge of where to obtain emergency contraception was good. In rural areas general practitioners may be the only source.

Our study reaffirms the findings of others showing poor knowledge of the correct time limit for using emergency contraception. Pearson *et al* quoted a figure of 22%[9] and George *et al* a figure of 13.6% for pregnant teenagers and women able to give the correct time limit.[8] It is encouraging, however, that 56% of sexually active girls in our survey gave the correct answer and that 31% had used emergency contraception. This may help to explain the constant abortion rates in the face of increasing sexual activity in the under 16s. In Scotland during 1989-93 the rate remained steady at 8.4 per 1000 girls aged 13-15.

We were not surprised to find that only 13.5% of pupils thought emergency contraception safer than regular use of the oral contraceptive pill. Many health professionals lack sufficient knowledge about emergency contraception[10] and may be unsure of the correct time limits and confused about safety, especially if it is used more than once. It is crucial that the under 16s believe that confidentiality exists between a doctor and patient when the patient requires contraceptive advice. In this study most of the pupils, including most of the girls, accepted this.

Sex education in schools is often criticised. However, in our study, school was the most commonly cited source of information about emergency contraception. Knowledge of details was poor, reflecting a view that generalities rather than specifics are provided by schools. The crucial part played by schools was shown recently in a structured school sex education programme which increased knowledge and reduced sexual activity.[11]

Health professionals were not a prominent source of information in this survey. Teenagers, however, attend their general practitioners two or three times a year,[12] which may be seen as a missed opportunity for promoting sexual health. An evaluation of the provision of contraceptive services in the United Kingdom showed the

**Key messages**

- More under 16s are sexually active than previously reported, especially those who are low achievers academically
- Under 16s have better awareness of the existence of emergency contraception than previously reported
- Despite good awareness of emergency contraception, teenagers have poor knowledge of specific details—particularly time limits and safety
- One third of sexually active girls aged under 16 have used emergency contraception
- Health education initiatives should concentrate on the practicalities of emergency contraception and target teenagers at particular risk

lowest pregnancy rates in areas where family planning clinics were available in addition to services provided in primary care, and this was especially noticeable in the under 16s.[13]

Health education initiatives should be directed towards teenagers who are at high risk of becoming sexually active at a young age and less well informed about emergency contraception. Smith suggested that areas of socioeconomic deprivation should be targeted.[14] Our study suggests that schools with lower academic attainment should also be included in this type of initiative.

## Conclusion

Emergency contraception has the potential to prevent unwanted pregnancies.[15] Most teenagers in Lothian are aware that emergency contraception exists. Use, however, will increase only when potential users believe it to be safe and know where to obtain it and when to use it. These aspects need to be tackled now. Schools and the media could be used more effectively to maximise the potential benefits of emergency contraception in the under 16s.

The questionnaire used in the survey may be obtained by writing direct to AG. We thank the schools, teachers, and especially the pupils who took part as well as Lothian Education for its cooperation. We also thank Fiona Sutter for help with computing, Ian Young (Health Education Board for Scotland) for help and advice, and Peter Brocklehurst (National Perinatal Epidemiology Unit, Oxford) for statistical advice.

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# Lifetime exposure to environmental lead and children's intelligence at 11-13 years: the Port Pirie cohort study

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**Abstract**

***Objective*—To examine the association between environmental exposure to lead and children's intelligence at age 11-13 years, and to assess the implications of exposure in the first seven years of life for later childhood development.**

***Design*—Prospective cohort study.**

***Subjects*—375 children born in or around the lead smelting town of Port Pirie, Australia, between 1979 and 1982.**

***Main outcome measure*—Children's intelligence quotient (IQ) measured at 11-13 years of age.**

***Results*—IQ was inversely associated with both antenatal and postnatal blood lead concentrations. Verbal, performance, and full scale IQ were inversely related to blood lead concentration with no apparent threshold. Multivariate analyses indicated that after adjustment for a wide range of confounders, the postnatal blood lead concentrations (particularly within the age range 15 months to 7 years) exhibited inverse associations with IQ. Strong associations with IQ were observed for lifetime average blood lead concentrations at various ages. The expected mean full scale IQ declined by 3.0 points (95% confidence interval 0.07 to 5.93) for an increase in lifetime average blood lead concentration from 0.48 to 0.96 μmol/l (10 to 20 μg/dl).**

***Conclusions*—Exposure to environmental lead during the first seven years of life is associated with cognitive deficits that seem to persist into later childhood.**

## Introduction

Many studies have reported inverse associations between low level lead exposure and neuropsychological development, particularly cognitive function.[1-7] The accumulation of this evidence has prompted public health authorities in several countries progressively to lower the blood lead concentrations at which environmental intervention and medical evaluation is warranted.[8,9] Since both Australian and American data indicate that the high childhood blood lead concentrations of 13-15 years ago are definitely decreasing,[10-12] a contemporary question of great interest is whether the effects of early exposure to lead still persist into later life when lead exposure is generally much lower.

The Port Pirie cohort study started in 1979. Within this cohort, the geometric mean blood lead concentration in the children increased from 8.3 μg/dl (0.40 mmol/l) at birth (umbilical cord blood) to 21.2 μg/dl (1.02 mmol/l) at age 2 years, and had decreased to 11.6

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# Screening for *Chlamydia trachomatis* infection is indicated for women under 30 using emergency contraception

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**Abstract**

A total of 838 women attending a large family planning clinic in Scotland for emergency contraception were offered screening for *Chlamydia trachomatis* infection. 569 were screened using ligase chain reaction test in first void urine at the time of presenting for emergency contraception and were retested 1 or 2 weeks later. Women aged under 20 and over 30 years were significantly more likely to decline to be tested than women aged 20 to 30. The prevalence of chlamydia was 7.6% in woman aged 24 or less, 5.3% in women aged 25 to 29, and 1.2% in women aged 30 or more. Only two women (< 1%) who tested negative at the time of using EC were positive 1 or 2 weeks later. Women under age 30 who use EC should be offered screening for chlamydia infection and testing at the time they attend for EC is adequate to detect the great majority of infected women. 

## 1. Introduction

Women who use emergency contraception (EC) do so because they have had unprotected sexual intercourse, sometimes with someone they do not know well. Unprotected intercourse risks sexually transmitted infection (STI). In the UK the most common bacterial STI is *Chlamydia trachomatis*. It is usually asymptomatic but is associated with potentially serious sequelae including pelvic inflammatory disease, ectopic pregnancy and infertility. Two UK guidelines suggest that opportunistic testing for chlamydia infection should be considered for all sexually active women aged under 25 years of age [1,2]. Targeted testing is recommended for specific groups such as patients attending genitourinary medicine clinics and women undergoing induced abortion [3]. Women using EC may represent a group that would be suitable for targeted chlamydia screening. However, hormonal EC must be given within 72 h of intercourse and, because it may be more effective the sooner it is used [4], women are encouraged to take it as early as possible after having sex. There are no data on how long after potential exposure it is best to test for *C. trachomatis*, but testing very soon after intercourse may be too early to allow detection. We undertook a study of the prevalence of chlamydia infection, and of the value of offering delayed testing, among a group of women requesting EC.

## 2. Participants and methods

Every woman presenting to a large family planning clinic in central Edinburgh for EC and who would be available for follow-up in the event of a positive result was offered screening for *C. Trachomatis* infection. Recruitment continued until 602 women agreed to participate in the study. Demographic characteristics; the number of hours elapsed since sexual intercourse; whether intercourse was with a regular partner; the reason for requiring EC; consistency of condom use; and past history of STI were recorded.

A first void specimen of urine was collected at the clinic visit and sent to the local laboratory for routine testing using a ligase chain reaction (LCR) (the LCx probe system Abbot Diagnostics, Maidenhead, UK). Women were asked to send a second urine specimen in a prepaid envelope direct to the laboratory either 1 week later (the first 300 women) or 2 weeks later (the second 302 women).

Women were informed of negative results by post. Positive results were telephoned to the patient who was asked to return to the clinic for treatment and contact tracing.

The study was approved by the local research ethics

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Table 1
Percentage of women testing positive for *C. trachomatis* infection, EC users and FP clinic attenders

| Age | <20 | 20–24 | 25–29 | ≥30 |
|---|---|---|---|---|
| Declined testing (%) | 34 (28) | 45 (17) | 52 (21) | 54 (27) |
| Number tested | 79 | 197 | 187 | 139 |
| Percent positive: EC users (n) | 7.6 (6) | 7.6 (15) | 5.3 (10) | 1.4 (2) |
| Percent positive: general FP (n) | 9.8 (244) | 8.4 (296) | 1.1 (363) | 1.2 (251) |

committee and informed, written consent was obtained from participants.

### 2.1. Statistical analysis

Data were analyzed with chi-squared tests using Yates correction for 2 × 2 tables and the test for trend to investigate association between binary and ordinal variables.

## 3. Results

The mean age of the 837 women requesting EC and offered screening was 26 years (range 13 to 46 years). The mean time since intercourse was 33 h. Forty-seven women would have been unavailable for follow-up and 188 declined to participate. The participation rate varied significantly between age group (Table 1), with more women in the youngest (under 20), and oldest age groups (30 and over), declining to participate ($\chi^2 = 8.93$, $p = 0.03$). The most common reason for refusal to enter the study was a recent test for chlamydia (42 women). There was no significant difference between the age groups in the number who claimed to have been recently tested. Thirty-three women considered themselves not to be at risk of infection, 16 of whom were aged 30 or over.

Five-hundred-ninety-six women produced a specimen of urine when they attended the clinic, six who were unable to pass urine when they were in the clinic said that they would hand in a specimen later that day but none did. Thirty-three women (5.5%) tested positive for chlamydia on their first test. Women under 30 were significantly more likely than older women to test positive ($\chi^2 = 4.67$, $p = 0.03$, 95% CI 1.21–42.4) (Table 1). The mean time since intercourse among women with a positive result was 33 h.

Women who had a positive test (16 women from the first 300 subjects and 17 women from the second 302) were informed of the result before they were due to send a second test specimen. One hundred eighty-seven women (66%) provided a second urine specimen 1 week later and 157 (55%) returned one 2 weeks later. Two women who tested negative for chlamydia infection at the time of the consultation for EC had a positive result in the second test (one after 1 week and one after 2 weeks). They had presented 28 and 70 h after intercourse. Both denied having sex with a different partner since using EC.

In 13 of the 344 women who produced a second urine specimen, the LCR sample/cut-off ratio increased from the first to the second test, but was nevertheless, considered and reported as negative. These women were asked to send a third specimen, eight women did so, one tested positive.

Three-hundred-seventy-four of the women tested for chlamydia infection (63%) used EC because of an accident with a condom. Three hundred sixty-two women said that they always used a condom, 4.7% of these tested positive for chlamydia; 6.5% of 168 women who sometimes used a condom tested positive, and 8.1% of women who never used a condom tested positive. These differences were not statistically significant. Eighty-four women had had a previous sexually transmitted infection (14%) and 100 (17%) had had sex with a new or 'not regular' partner. There were no significant differences in the prevalence of chlamydia infection according to history of STI or 'regularity' of partner.

## 4. Discussion

We have only been able to find one other report of the prevalence of chlamydia infection among women using EC. None of 135 Swedish women aged under 25 presenting to a clinic requesting EC tested positive [5]. In contrast, prevalence rates of *C. trachomatis* infection among women under 30 attending the Edinburgh clinic were similar to those found among Scottish women [3] undergoing induced abortion (5.6%). In a study of 507 women attending a family planning service in Aberdeen [6], the overall prevalence of infection was 5.1%. Ten percent of women under 20, but only 2.6% of women aged 20 to 24, and 1.4% of women aged 25 to 29, tested positive for infection. While our study was being undertaken we were also participating in a national Scottish study designed to determine the prevalence of *C. trachomatis* in women attending family planning (FP) clinics for contraceptive advice. The same LCR test was used by the same laboratory. The prevalence of chlamydia detected in the general FP clinic is shown in Table 1. Women under 25 and those aged 30 or more who presented for EC in our study were not more likely to screen positive for *C. trachomatis* than women attending the general FP clinic. However, women aged 25 to 29 using EC were significantly more likely to test positive than women in this age group attending for general FP advice ($\chi^2 = 9.06$, $p = 0.003$, 95% CI for odds ratios 1.71–38.7). It seems likely that women under the age of 25 who require EC have sexual lifestyles which are little different from those of their peers (who do not need to use EC) since they seem to be at no different risk of STI. For women aged 25 to 29, however, those who present for EC are at higher risk of infection than their peers who are perhaps more likely to be in stable monogamous relationships.

Although inevitably some women chose not to send in a

urine sample for a second test, 66% did so after 1 week and 55% after 2 weeks. Only two women who had a negative test at the time of using EC tested positive for chlamydia on repeat testing. A third woman tested positive 3 weeks later. This detection rate does not justify the time, expense and likely compliance involved in offering delayed testing.

Prevalence rates as low as 3% have been proposed as cost-effective for screening [7,8]. Women under 25 would automatically be screened if the Scottish Intercollegiate Guidelines Network (SIGN) guidelines were followed. Women aged 25 to 29 would not, but a prevalence rate of 5.3% does justify targeted screening of women in this age group presenting for EC.

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# THE EFFECTS OF SELF-ADMINISTERING EMERGENCY CONTRACEPTION

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## ABSTRACT

*Background* Emergency postcoital contraception prevents pregnancy, but it must be prescribed by a doctor and taken within 72 hours of intercourse. It has been proposed that emergency contraception be made available without a prescription. We undertook a study to learn how women might behave if given a supply of emergency contraceptive pills to keep at home.

*Methods* We assigned 553 women to be given a replaceable supply of hormonal emergency contraceptive pills to take home (the treatment group) and 530 women to use emergency contraception obtained by visiting a doctor (the control group). The frequency of use of emergency contraception, the use of other contraceptives, and the incidence of unwanted pregnancy were determined in both groups of women one year later.

*Results* The results for 549 women in the treatment group and 522 women in the control group were available for analysis. Three hundred seventy-nine of the women in the treatment group (69 percent) and 326 of the women in the control group (62 percent) contributed detailed information at follow-up. One hundred eighty of the women in the treatment group (47 percent) used emergency contraception at least once. Among those who returned the study questionnaire, 98 percent used emergency contraception correctly. There were no serious adverse effects. Eighty-seven women in the control group (27 percent) used emergency contraception at least once ($P<0.001$ for the comparison with the treatment group). The women in the treatment group were not more likely to use emergency contraception repeatedly. Their use of other methods of contraception was no different from that of the women in the control group. There were 18 unintended pregnancies in the treatment group and 25 in the control group (relative risk, 0.7; 95 percent confidence interval, 0.4 to 1.2).

*Conclusions* Making emergency contraception more easily obtainable does no harm and may reduce the rate of unwanted pregnancies. (N Engl J Med 1998;339:1-4.)



THE widespread use of emergency postcoital contraception could prevent 1.7 million unintended pregnancies and 0.8 million abortions each year in the United States.[1] Emergency contraception has been licensed in the United Kingdom since 1984. Although many women know that it is available,[2,3] it is underused because the method must be prescribed by a doctor and taken within 72 hours after intercourse. Medical consultation may be hard to arrange on short notice, and many women are embarrassed to ask their family doctors for emergency contraception.

Although in some countries health ministers have considered making emergency contraception available without a prescription and selling it in pharmacies,[4,5] for several reasons this has not yet happened. Pharmaceutical companies worry about litigation. Pharmacists are concerned about requests from girls under 16 years of age (the legal age of consent to sexual relations in the United Kingdom). Many doctors and the public believe that easy access to emergency contraception would encourage promiscuity and unsafe sexual relations and discourage the use of more reliable contraception.

However, the benefits of making hormonal emergency contraception available without a prescription may outweigh the difficulties. With this in mind, we investigated how women might behave if emergency contraception were more readily available and the effect that such availability might have on the number of unintended pregnancies.

## METHODS

We studied 1083 women, 16 to 44 years old, who were attending a family-planning clinic and a large hospital in Edinburgh, Scotland, from January 1994 through December 1996. Six hun-

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dred fifty women were recruited at their follow-up consultations after using emergency contraception, and 433 after therapeutic abortion. Women in whom estrogen was contraindicated (those with a history of arterial disease, venous thromboembolism, or severe migraine) were excluded.

After a routine consultation during which future contraception was discussed and contraceptive agents provided, the women who agreed to participate in the study were assigned to the treatment or control group on the basis of their dates of birth (women whose birthdays fell on even-numbered days were assigned to the treatment group). The women in the treatment group were given one packet of emergency hormonal contraceptive tablets to keep at home (four tablets, each containing 50 μg of ethinyl estradiol and 0.25 mg of levonorgestrel [Schering PC4, Schering Health Care, Burgess Hill, West Sussex, United Kingdom]), with instructions to take two tablets within 72 hours after intercourse and two tablets 12 hours later. They were also given written instructions and a telephone number to call in case they had questions. If emergency contraception was used, the women were instructed to mail a notification form to the clinic, with the time of intercourse, the time the pills were taken, and the date of the last menstrual period recorded. They also were instructed to come to the clinic within one week after the date of the expected next menstrual period, at which time the details of the emergency contraceptive use were verified and a pregnancy test was performed if indicated. If the woman was not pregnant, future contraception was discussed; if she wished to continue taking part in the study, she was given a replacement packet of emergency contraceptive pills and notification forms.

The women in the control group were simply informed of or reminded about how to use emergency contraception and where to get it and that it was safe to use it more than once. They were given a notification form to mail in if they used emergency contraception at any time during the next year.

All the women in both groups were sent a questionnaire after one year asking about the details of their use of contraception (including emergency contraception), about any pregnancies, whether they thought emergency contraception should be available without prescription, and how much they would be willing to pay for it. If the questionnaire was not returned, two additional questionnaires were sent. If we did not receive a response, we contacted the woman's family doctor to obtain information about her use of contraception and whether she had become pregnant. If the family doctor could not provide the information, the woman was deemed lost to follow-up and the information was sought from the Information and Statistics Division of the Scottish Health Department (to which all births and therapeutic abortions are reported) to determine whether she had been pregnant during the year.

The study was approved by the Lothian Research Ethics Committee with the stipulation that women using emergency contraception more than four times in four months be withdrawn from the study. All the women gave informed consent.

### Statistical Analysis

Differences between the groups were tested by chi-square tests with Yates' correction for binary factors or Mann–Whitney tests for ordinal factors.

## RESULTS

The results for 1071 women (549 in the treatment group and 522 in the control group) were available for analysis. One woman was withdrawn from the study because she used emergency contraception more than four times in four months. One woman in the control group died in a traffic accident, and 10 women (3 in the treatment group and 7 in the control group) dropped out of the study for personal reasons. None of these women had used emergency contraception before they left the study.

**TABLE 1.** CHARACTERISTICS OF THE WOMEN IN THE TREATMENT AND CONTROL GROUPS AND INFORMATION ABOUT FOLLOW-UP.*

| VARIABLE | TREATMENT GROUP | CONTROL GROUP |
|---|---|---|
| | no. (%) | |
| No. enrolled in study | 553 | 530 |
| Recruited after use of emergency contraception | 323 (58) | 327 (62) |
| Recruited after abortion | 230 (42) | 203 (38) |
| Age | | |
| <20 yr | 132 (24) | 116 (22) |
| 20–29 yr | 314 (57) | 309 (58) |
| >30 yr | 107 (19) | 105 (20) |
| Age full-time education ended | | |
| <16 yr | 93 (17) | 92 (17) |
| 17–18 yr | 127 (23) | 106 (20) |
| 19–22 yr | 116 (21) | 114 (22) |
| ≥23 yr | 54 (10) | 61 (12) |
| Still in school full time | 154 (28) | 145 (27) |
| Educational status unknown | 9 (2) | 12 (2) |
| No. with results available for analysis | 549 | 522 |
| Final questionnaire returned | 379 (69) | 326 (62)† |
| Information from family doctor | 136 (25) | 152 (29)‡ |
| Lost to follow-up | 34 (6) | 44 (8)‡ |

*Because of rounding, all percentages do not total 100.

†P=0.03 for the comparison between the groups.

‡P=0.12 for the comparison between the groups.

The characteristics of the women in the two groups were similar (Table 1). The women in the treatment group were more likely to return their final questionnaires (P=0.03). The women returning the final questionnaire were older (P<0.001) and more likely to have been recruited after use of emergency contraception than after an abortion (P<0.01). There was no effect of education on whether the women returned the questionnaires (P=0.52).

The women in the treatment group were significantly more likely to use emergency contraception on only one occasion than those in the control group (36 percent vs. 14 percent, P<0.001) (Table 2) but not more likely to use it more than once (12 percent [45 of 379 women] vs. 13 percent [42 of 326 women], P=0.77). Correct use of emergency contraception was determined from the notification forms, 91 of which were returned. The only woman who used emergency contraception incorrectly had lost the instruction sheet and did not take the second dose.

Twelve pregnancies were reported to have begun during a cycle in which emergency contraception had been used. Given that it was used on a total of 387 occasions (248 times by women in the treat-

**TABLE 2.** USE OF EMERGENCY CONTRACEPTION AMONG THE WOMEN IN THE TREATMENT AND CONTROL GROUPS WHO RETURNED THE FINAL QUESTIONNAIRE.

| USE OF EMERGENCY CONTRACEPTION | TREATMENT GROUP (N=379) | CONTROL GROUP (N=326) |
|---|---|---|
| | no. (%) | |
| Did not use | 199 (53) | 239 (73) |
| Used once | 135 (36) | 45 (14)* |
| Used twice | 27 (7) | 33 (10) |
| Used three times | 13 (3) | 8 (2) |
| Used more than three times | 5 (1) | 1 (<1) |

*P<0.001 for the comparison between the groups.

**TABLE 3.** PATTERNS OF CONTRACEPTIVE USE AT RECRUITMENT AND ONE YEAR LATER AMONG THE WOMEN IN THE TREATMENT AND CONTROL GROUPS WHO RETURNED THE FINAL QUESTIONNAIRE.*

| METHOD OF CONTRACEPTION | TREATMENT GROUP | | CONTROL GROUP | |
|---|---|---|---|---|
| | AT RECRUITMENT (N=350) | ONE YEAR LATER (N=350) | AT RECRUITMENT (N=336) | ONE YEAR LATER (N=336) |
| | number (percent) | | | |
| Oral contraception | 45 (13) | 169 (48) | 46 (14) | 171 (51) |
| Condom | 258 (74) | 108 (31) | 235 (70) | 94 (28) |
| Diaphragm | 7 (2) | 7 (2) | 11 (3) | 15 (4) |
| Combination | 3 (1) | 31 (9) | 6 (2) | 34 (10) |
| None | 34 (10) | 21 (6) | 33 (10) | 15 (4) |
| Other or no answer | 3 (1) | 12 (3) | 5 (1) | 6 (2) |
| Pregnant | 0 | 2 (1) | 0 | 1 (<1) |

*The number of women in each treatment group is the number who responded to the question regarding the method of contraception.

ment group and 139 times by women in the control group), this represents a failure rate of 3 percent, which is within the range reported in routine clinical practice.[6] There was no report of any serious illness after the use of emergency contraception.

The condom was the most common method of contraception at the start of the study (Table 3). During the subsequent year, many women in each group abandoned condoms in favor of hormonal contraception, but there was no significant difference between the groups (P=0.07). Eighty-nine percent of the women in the treatment group said that their use of other methods of contraception was unaffected, and 8 percent reported that the availability of emergency contraception gave them "peace of mind," but 2 percent said that they took more risks.

Data on pregnancies were available from three sources — the follow-up questionnaires, the women's family doctors, and the Scottish Health Department. It was not possible to determine whether every pregnancy was intended. There were 28 pregnancies among the 549 women in the treatment group (5 percent) and 33 pregnancies among the 522 women in the control group (6 percent) during the year of follow-up (Table 4). Eight women in the treatment group and four in the control group appear to have conceived during a cycle in which emergency contraception was used; all these pregnancies were terminated, accounting for 53 percent of the abortions in the treatment group and 21 percent in the control group. A total of 18 pregnancies in the treatment group were known to have been unintended, as compared with 25 in the control group (relative risk, 0.7; 95 percent confidence interval, 0.4 to 1.2).

Among the women for whom detailed information at follow-up was available (379 in the treatment group and 326 in the control group), more of those in the treatment group (299 [79 percent]) thought

**TABLE 4.** PREGNANCIES DURING THE YEAR OF FOLLOW-UP IN THE TREATMENT AND CONTROL GROUPS.

| VARIABLE | TREATMENT GROUP (N=549) | CONTROL GROUP (N=522) |
|---|---|---|
| | no. (%)* | |
| Total no. of pregnancies | 28 (5) | 33 (6) |
| Abortions | 15 (3) | 19 (4) |
| Pregnancies despite use of emergency contraception | 8 | 4 |
| Childbirths | 11 | 11 |
| Known planned pregnancies | 8 | 6 |
| Known unintended pregnancies | 2 | 4 |
| Miscarriages | 2 | 3 |
| Known unintended pregnancies | 1 | 2 |
| Total no. of unintended pregnancies | 18 (3) | 25 (5) |

*Percentages are shown for key outcomes.

that emergency contraception should be available without a prescription than was the case in the control group (198 [61 percent], P<0.001). This was particularly true among the women who had entered the study after having had an abortion. There was no effect of age on the women's views. Many of the women (42 percent in the treatment group and 52 percent in the control group) were willing to pay £5 (about $8) for emergency contraception, and more than 68 percent in both groups said they would pay £3 (about $5).

## DISCUSSION

The results of this study suggest that making emergency contraception available at home is safe and may reduce the risk of unintended pregnancy. However, it is important to note that we studied a well-defined group of women who we thought were likely to use emergency contraception because they had used it previously or because they had terminated a pregnancy. Furthermore, the women were well educated (less than 20 percent had left school before the age of 16 years, and half had gone to a university or college) and were likely to have a responsible attitude toward contraception. Nevertheless, we think the study suggests what might happen if emergency contraception were made available without a prescription.

Emergency contraception is not universally available. It is not licensed, for example, in France or the United States. However, some brands of combined oral contraceptives contain the same hormones as the preparation we used, and although not licensed for such use, these contraceptives can be used as a substitute. Many clinics in the United Kingdom routinely use these oral contraceptives for emergency contraception because they are considerably cheaper than the marketed preparation we used, and many women have supplies of oral-contraceptive pills at home and could make up their own emergency contraceptive regimen if they knew how. Indeed, in 1997 the U.S. Food and Drug Administration announced that six brands of commonly used combined oral contraceptive pills are safe and effective for use as emergency postcoital contraceptives.[7]

It has been argued that if emergency contraception were available without a prescription, women would not use it correctly. We found, however, that most of the women did use it correctly, including many who were recruited after abortions and had never used such contraception before. It is also possible that women might use emergency contraception when they are already pregnant. We cannot test this hypothesis. A small number of women in our study conceived during the cycle in which they used emergency contraception, and it is possible that some of them were already pregnant when they took the tablets. Even if it was used during pregnancy, either in error or intentionally in the mistaken belief that it might cause an abortion, it would almost certainly have done no harm. The estrogen–progestin regimen of emergency contraception is ineffective after implantation, and there is no evidence that it is teratogenic.[8]

It has also been argued that if emergency contraception were more readily accessible, women might use it repeatedly and abandon more reliable methods of contraception. However, very few of the women in the treatment group used it more than once, and they were not more likely to do so than the women in the control group who had to visit a doctor to obtain it. Nor did improved accessibility affect the pattern of contraceptive use. Few women said that they took more risks, and during the study similar numbers in each group switched from using barrier methods to using more reliable oral contraception.

Although the incidence of unintended pregnancy was lower among the women who had emergency contraception available at home than among those who had to obtain it from a doctor, the sample was small and the difference was not statistically significant. The reduction in the number of unintended pregnancies might have been greater if we had given more than one packet of pills to each woman. Although 135 women used emergency contraception once, only 74 returned to the clinic for another packet.

This study suggests that women are able to self-administer emergency contraception correctly, at the appropriate time, and without adverse effects. Given the opportunity to keep the necessary tablets at home, most of the women found emergency contraception a useful addition to their contraceptive options. Although many of the women thought that it should be available without a prescription, they did not appear to abandon more reliable methods of contraception in favor of the repeated use of emergency contraception. Making emergency contraception more accessible may reduce the rate of unintended pregnancies.

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# Advanced provision of emergency contraception has not reduced abortion rates in Lothian

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**Abstract**

A number of small studies have demonstrated increased use of emergency contraception (EC) when women have a supply available at home. It has been suggested that widespread use of EC could reduce abortion rates. We undertook a community intervention study designed to determine whether offering advanced supplies of EC to large numbers of women influenced abortion rates. Women aged between 16 and 29 living in Lothian, Scotland were offered, through health services, five courses of EC to keep at home. 17831 women took a supply of EC home and over 4500 of them gave at least one course to a friend. 45% of women who had a supply used at least one course. In total an estimated 8081 courses of EC were used. More than 75% of EC was used within 24 hours of intercourse. Abortion rates in Lothian were compared with those from three other health board areas of Scotland. No effect on abortion rates was demonstrated. The enthusiasm for distributing advanced supplies of EC through health services may be misplaced as a strategy to reduce unintended pregnancy in the UK.

## Introduction

Unintended pregnancy is common and abortion rates are rising worldwide. Emergency contraception (EC) may prevent up to 95% of unwanted pregnancies [1]. It is increasingly regarded as a means to reduce abortion rates [2,3]. Considerable effort and funding are being spent making EC available in countries where it is not yet licensed [4], promoting it in countries where it is, [5] and relaxing restrictions on its provision[6]. But would improving access to emergency contraception really prevent large numbers of pregnancies ?

If EC was used whenever it was indicated, it has the theoretical potential [7]to reduce abortions in Scotland from around 12,000 to 4,000 each year. Although most women of reproductive age in Scotland know about EC [8,9], only 1.9% of Scottish women aged 16-44 used it during 2001 [10]. In a small study undertaken in Edinburgh [11,]advanced provision of EC significantly increased its use. Encouraged by these findings, the Lothian Emergency Contraception Project (LECP) was undertaken to see whether giving large numbers of women supplies of EC to keep at home would reduce abortion rates.

## Materials and Methods.

### i. Participants

The project took place in the county of Lothian in South East Scotland. Everyone resident in Scotland can register with a general practitioner (GP, family doctor) who provides primary healthcare, including contraception, free of charge. Contraceptive supplies are not subject to prescription charges. Emergency contraception has been licensed in the UK since 1984.

All health providers in Lothian likely to prescribe emergency contraception were invited to participate . This included all (124) general practices, 17 community family planning (FP) clinics, the gynaecological and genito-urinary medicine (GUM) departments of the main hospital (The Royal Infirmary of Edinburgh) and Brook Scotland, a non-governmental sexual health service for young people. Supplies of EC were also offered to new college students at 'Fresher's Fairs' at the start of the academic year in autumn 2000.

All women aged 16-29 years who lived in Lothian were to be offered five courses of Schering PC4 (Schering Healthcare, England) to keep at home. PC4 (ethinyl oestradiol and levonorgestrel) was the only EC product available in 1999 and had to be prescribed by a doctor. The five courses and a detailed information/instruction leaflet were packaged in one box. Women who were sterilised or using an intrauterine device or contraceptive implant were excluded from the study. The project was advertised widely with the intention that women themselves would ask for a supply of EC when attending for routine healthcare. Publicity materials - information leaflets and posters - were distributed to GP surgeries, participating clinics, libraries, cinemas, hairdressers, community pharmacies, night-clubs, pubs (bars) and discotheques, and posters were displayed in public toilets. A press conference for the local and national media launched the study. Every invitation for

media publicity was accepted. Nine months into the study every household in Lothian was mailed a postcard inviting women to ask their doctor for supplies of emergency contraception to keep at home.

ii. **Data collection.**

A record of the number of project supplies sent to each participating centre was held centrally and centres kept a record of the number of women receiving a box of EC (five courses). These records revealed how many women received a supply of EC to keep at home.

A questionnaire was designed to determine, among a sample of women eligible to receive supplies, how many had been offered (and accepted) EC and whether and how they had used it. Purposive sampling was used to select ten of the participating general practices representing a range of socio-economic characteristics and location. The questionnaire was mailed to all 6,486 women aged 16-29 years registered with the 10 practices after the project had been running for 18 months. One reminder was sent to non-respondents (one practice declined to send a reminder). Using a similar questionnaire, patterns of use of EC were also investigated among a random sample of 310 women who had received a home supply from a FP clinic.

As part of the evaluation, in depth interviews were conducted with a sample of women who received project supplies of EC and with professional staff in case study practices. These will be reported elsewhere. To determine the effect of the intervention, annual abortion and birth rates [12] from 1998 to 2001 were compared between Lothian and three other large Scottish Health Board areas (Grampian, Tayside and Greater Glasgow) using routine data collected by the Information and Statistics Division (ISD) of the Scottish Health Service. Abortion referral rates during 1999, 2000 and 2001 from individual general practices in Lothian were compared using data from the centralised Lothian Abortion Referral Service [13]. Ethical approval for the study was obtained from the local research ethics committee.

**iii. Analysis.**

Total abortion rates in 1998/9 and 2000/1 between Lothian and other health boards were compared using multiple logistic regression. Referrals for abortion in 1999, 2000 and 2001 between groups of general practices in Lothian were compared using two- sample T-tests using a logarithmic transformation to achieve approximate normality. Patterns of acceptance and use of EC were examined through frequencies of response from the two questionnaires.

Characteristics of those who received advance supplies of EC were identified using questionnaire data from women registered at case study practices. The intra- class correlation co-efficient estimated from a variance components model based on 2,629 respondents suggested that around 10% of the total variability in the outcome occurred at practice level. A multilevel model was therefore constructed using MlwiN software

(Version 1.10.0006) to predict whether or not the respondent received advance supplies of emergency contraception. The individual explanatory factors included in the model were: age (years); highest qualification (five-way categorical scheme: still at school; vocational qualifications; High School equivalent qualifications at age 17-19; degree / postgraduate; and 'other'); employment status (three-way categorical scheme: full-time paid employment; full-time student; and all others); co-residency (binary: living alone or with unrelated others; all other states); housing tenure (three-way categorical scheme: privately owned; rented from Public Housing Organisations; and 'other'); and past use of emergency contraception. Due to the effects of multiple missingness the final model is based on data from 2,294 (87.3%) respondents. Only associations significant at 0.01% are reported in this paper.

## Results

Ninety-seven general practices in Lothian and all the other services providing EC, participated. Six months into the study it became clear that women were not asking for advance supplies of EC. Since they appeared enthusiastic about taking a supply home if actively offered, centres were asked to be more pro-active . Newsletters were sent regularly to centres to encourage recruitment.

### i. Number of women receiving advanced supply of EC

The project ran from 1st September 1999 to 31st December 2001. When it closed a supply of emergency contraception had been distributed to 17,831 women (table 1). There was a wide variation in the number of packets distributed by the general practices (table 2).

From the general practice survey, 943 questionnaires were returned undelivered, 2,817 women responded – a rate of 50.8%. 188 questionnaires were blank, leaving 2,629 for analysis. 286 women (92%) completed the FPC questionnaire. 361 (13.7%) of respondents to the GP questionnaire reported receiving project packs of EC. Only age (odds ratio: 0.94; 99% CI 0.88 – 0.99) and receipt of EC prior to September 1999 (odds ratio: 2.58; 99% CI 1.83 – 3.62) were significantly associated with receipt of project EC ($p = 0.01$).

Of the women responding to the questionnaires, 116 (32.1%) of the GP practice sample and 60 (21%) of the FP sample reported giving away at least one packet of EC. Assuming that 26% (the mean of the two samples) of women receiving packets from the other project sources (table 1) also gave supplies away, we estimate that some 4772 women received at least one course of EC from a friend. Thus a total of at least 22,603 women had access to EC without needing to see a doctor.

### ii. Use of EC

53.3% of women who received a project supply of EC from their GP were given it at the time they presented needing emergency contraception, leaving four courses to keep at

home. Most women receiving supplies from an FP clinic were not attending for EC, however those who were, received the home supply in addition to the treatment required. Fifty per cent of respondents to the GP survey who had received an advance supply of EC, and 40% of women responding to the FPC survey used at least one course of the five supplied. Overall we estimate that at least 8081 courses of EC were used. It seems likely that most of the 4772 women who received EC from a friend were given it because they needed it. A total of over 12,000 courses of EC may therefore have been used in Lothian through the project.

Of 647 women who reported receiving EC to keep at home on the questionnaires, thirty-six (5.5%) reported unintended pregnancies. Only eight reported using EC in an attempt to prevent the pregnancy.
294 women reported using at least one course of EC. Of these 75.7% of courses were used within 24 hours, and 51.8% less than 12 hours, after unprotected intercourse. Respondents completing the GP practice questionnaire who had a home supply of EC were more likely to be using hormonal contraception (oral or injectable) at the time of completing the questionnaire, than at the time of receiving supplies (table 3).

### iii. Effect on abortion and birth rates

No significant differences were seen for any health board area in the total abortion rates (women aged 16-44) or the rates for women aged 16-29 (table 4) when 1998 or 1999 were compared with 2000 or 2001. Using an interaction model, the multiple logistic regression gave a 95% confidence limit of –6% to +10% for the difference between Lothian and Grampian in the change in abortion rates between 1998-1999 and 2000-2001. There were no significant differences in changes in birth rates between the various health boards over the same years (data not shown).
There were no significant differences in the mean number of women referred for termination of pregnancy during 1999-2001 between the 10 practices distributing the most packets of EC, the 10 practices distributing fewest packets and the 7 who did not participate in the project (table 5).

## Discussion

Offering advance supplies of emergency contraception appears to have had no effect on abortion rates in Lothian. This study is the sixth, and by far the largest, to show that advanced provision of EC increases its use [11,14,15,16,17]. Moreover this study, like one other [17], has demonstrated much earlier use of EC, thought to increase efficacy [18]. In the present study over 75% of women who had used an advance supply of EC had used it within 24 hours, in contrast to the average 38 hours taken to access it through a FPC [19].
If at least 18000 young women in Lothian had easy access to EC, were more likely to use it and to use it quickly, why was there no measurable effect on abortion rates ? Abortion rates are influenced by many factors and fluctuate from year to year. An effect of a single event, even a major one like the third generation 'pill scare' of 1995, is hard to

demonstrate convincingly [20]. Abortion is a relatively uncommon event in Scotland. Fewer than 2000 of the 85000 women aged 16-29 in Lothian will have an abortion each year. For this reason, and despite knowing that they are notoriously hard to do [21], we chose a community intervention study in order to get supplies of EC to large numbers of women. Almost one in four of our target group took at least four courses of EC home. They were young, sexually active, and nearly 54% of those receiving supplies from their GP were using condoms. A lot of EC was given away. With an abortion rate of 24/1000 (table 4) we would have expected some 530 abortions among the women who had a supply of EC at home, but the intervention does not appear to have prevented even half of them. Perhaps simply not enough women took a supply home. Although some general practices issued supplies to a lot of women, many health professionals did not promote the project to women who were not consulting for emergency contraception. Women themselves reported finding it difficult to ask for EC proactively. Several other studies have drawn attention to health professionals [22,23] and women's concern [24] about deregulation and repeated use of EC. Although most women were pleased to accept a supply of EC to keep at home when offered, very few actually asked for a supply, even in the FPC where notices were displayed prominently.

Were advance supplies given to the right women ? The LECP made EC available almost exclusively through health services and most often to women who had already consulted for EC or for other contraception. In so doing, it may not have reached women most at risk of unintended pregnancy – those using no contraception or using condoms inconsistently who do not access contraceptive services.

Perhaps having a supply of EC so easily available encouraged women to take more risks with unprotected intercourse. As with our pilot study however, women tended to move from less effective methods of contraception (mainly condoms) to more effective methods (hormonal) during the period of follow up (table 3). Moreover, we asked women in the questionnaire surveys whether they felt that they were less careful about contraception and the vast majority said they were not. It seems unlikely then that pregnancies prevented by EC among women who used it were matched by pregnancies arising from increased risky sexual behaviour.

Perhaps the most likely explanation for the failure to influence abortion rates lies in the observation that even when women did have EC at home, it was not always used when it might have prevented a pregnancy. 74% of the 36 women who had advance supplies and reported an unintended pregnancy did not use EC. Many women have a 'low sense of vulnerability towards pregnancy' [25], even when they know that they have taken risk. In a number of studies in different countries among women having abortions [2, 26,27], the failure to recognise a risk of pregnancy is the commonest reason for non-use of contraception including EC. Having a supply of EC to keep at home will not help women who do not recognise the risk of pregnancy, and therefore do not recognise the need to use EC.

Were we expecting too much of the intervention in this setting ? Contraceptive prevalence is high in Scotland and abortion rates are relatively low. It has been estimated however that in the UK some 70% of pregnancies are preventable [27] (contraception not used or used incorrectly or inconsistently), so even although the absolute number of unintended pregnancies is relatively small, there is plenty of opportunity for EC use. It is

possible that in other settings, where contraceptive prevalence is low, abortion rates high and women relatively naive about EC, advanced provision may reduce the public health cost of unintended pregnancy.
Finally, it is possible that emergency contraception may be less effective than we think. Estimates of efficacy are something of a guess, based on rather unreliable data and a great many assumptions [28] and have been questioned both in the past [29] and more recently [30].

Whatever the shortcomings of this study, the fact remains that multiple courses of emergency contraception were made available to a large number of women in advance of need. More than 17,000 of them took it home and over 8000 (perhaps as many as 12000 if those who obtained EC from a friend are included) used it, yet no impact on abortion rates was measurable. While advanced provision of EC probably prevents some pregnancies for some women some of the time, the strategy did not produce the public health breakthrough hoped for. The prospect of reducing abortion rates by widening access to EC through health services seems somewhat diminished by the findings of this study.

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| **Table 1**: Number (and percentage )of project packs distributed by participating services | |
|---|---|
| **Service** | **Number (%)** |
| Family planning clinics | 6,549 (36.7) |
| Brook Scotland | 924 (5.2) |
| Hospital clinics | 2,025 (11.4) |
| General Practices | 7,708 (43.2) |
| "Freshers' Fair" | 625 (3.5) |

| **Table 2**: Number of general practices distributing specific numbers of project packs | |
|---|---|
| **Number of packs distributed** | **Number of practices** |
| <10 | 7 |
| 10-19 | 7 |
| 20-49 | 17 |
| 50-99 | 30 |
| 100-200 | 20 |
| >200 | 5 |
| No information provided | 7 |

NB. Two practices hold two separate branch surgeries which are counted individually in the list of 124 Lothian Practices but functioned as a single practice during the project thus the total number of practices listed here is 93.

| **Table 3: Main method of contraception used by GP survey respondents and national sample** | | | | | |
|---|---|---|---|---|---|
| | **Case study practices respondents (%)** | | **National sample (%) (Oddens 1994 [31])** | | |
| **Method** | On receipt of project EC | On completing questionnaire | age 15-19 | age 20-24 | age 24-29 |
| Oral contraceptive | 33.5 | 48.8 | 64.4 | 69.7 | 51.7 |
| Contraceptive injection | 0.6 | 4.1 | | | |
| Barrier methods | 54.1 | 30.0 | 26.6 | 21.1 | 20.4 |

**Table 4.** Number (and rates) of abortions among women aged 16-29 in Scotland as a whole and in the four major health board areas from 1998 – 2001.

| | **1998** | **1999** | **2000** | **2001** |
|---|---|---|---|---|
| **Scotland** | 8882 (18.9) | 8542 (18.5) | 8368 (18.5) | 8453 (18.7) |
| **Lothian** | 1915 (24.2) | 1913 (24.3) | 1769 (22.4) | 1849 (23.4) |
| **Grampian** | 1009 (21.4) | 936 (20.3) | 857 (19.3) | 848 (19.1) |
| **Greater Glasgow** | 1655 (17.4) | 1613 (17.3) | 1582 (17.1) | 1643 (17.8) |
| **Tayside** | 882 (26.6) | 791 (24.6) | 829 (26.7) | 750 (24.1) |

**Table 5.** Total number of project supplies of EC issued and total number of women referred for abortion 1999-2001 among the 10 best performing (distributed supplies to the most women) and 10 worst performing (distributed supplies to the fewest women) general practices and seven practices that did not participate

| **Practices** | **Total EC supplies** | **Total abortion referrals** | | |
|---|---|---|---|---|
| | | **1999** | **2000** | **2001** |
| **Best performance** | 2880 | 292 | 219 | 298 |
| **Worst performance** | 239 | 70 | 63 | 66 |
| **Non participants** | 0 | 90 | 93 | 107 |

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**Emergency Contraception (EC): why can't you give it away? Qualitative findings from an evaluation of advance provision of EC.**

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**Abstract**

**Objectives.** To explain why the Lothian Emergency Contraception Project (LECP) – a primary care based intervention to offer advance supplies of emergency contraception (EC) to women aged 16-29 was not associated with a reduction in abortion rates.

**Design.** Case studies, utilising qualitative and quantitative methods, were used to evaluate the intervention. In this paper findings from qualitative interviews are presented.

**Setting.** 10 general practices, purposively chosen to represent a range of socio-economic characteristics, geographical locations and enthusiasm for the intervention, and the central family planning clinic in Lothian.

**Participants.** 44 primary care professionals working at general practice case study sites and 22 women who had received advance supplies.

**Results.** Professionals reported that women rarely asked for advance supplies of EC, and they were reluctant to offer supplies to women other than when they consulted for emergency contraception. Their reluctance was underpinned by concerns about contradictory sexual health messages implied by the offer; a perceived association of EC use with chaotic behaviour by women; views about the sort of women suitable for advance supplies; and practical difficulties making the offer. Some women reported surprise at the offer of advance supplies but most recognised benefits of having EC at home for themselves. Nevertheless they were reluctant to ask for advance supplies because of misgivings about the appropriateness of offering advance supplies to everybody and concerns about being judged by health professionals as morally inadequate.

**Conclusions.** As women themselves are unlikely to seek out advance supplies, advance provision of EC may only be successful in reducing abortion rates if professionals address their own concerns about EC and develop ways to encourage women not already accessing or using EC or other contraception to take supplies.

## Introduction

Concerns about the high rate of unintended pregnancy in the UK have prompted the relaxation of restrictions on the provision of emergency contraception including free pharmacy provision in some areas of multiple deprivation (known as Health Action Zones in England) and the removal of prescription only status to allow its supervised sale at commercial rates through community pharmacies[1]. The Lothian Emergency Contraception Project was an alternative radical initiative designed to increase use of emergency contraception by providing multiple courses to women in advance of need. The project, which is reported in detail elsewhere[2], involved advance supplies of 5 courses of Schering PC4 being made available to all women aged 16-29 resident in Lothian with the express aim of reducing pregnancy termination rates. Women were encouraged to collect advance supplies from participating centres, and professionals working in these centres were encouraged to offer supplies to eligible women.

It was clear that the success of the project was likely to be dependent upon adequate distribution of advance supplies to the eligible women and in particular those most at risk of unintended pregnancy, and appropriate use of supplies by women once they had them. We have shown that sufficient numbers of packs of EC appear to have been distributed to have had an impact on abortion rates and that women who used their advance supplies reported doing so in a timely fashion and not forsaking more reliable methods of contraception. Yet no impact upon abortion rates was observed[2]. We have also shown that the majority of women who received advance supplies had either previously used EC or were given the extra supplies when they consulted for EC[2]. Women who have already consulted for EC are not likely to be those with the greatest problems of access to contraception, and may not be typical of the population most at risk of unintended pregnancy. This suggests that whilst distribution of advance supplies of EC in the Lothian Emergency Contraception Project was theoretically sufficient to impact upon abortion rates in Lothian, in practice it may have been inadequately targeted at women at risk of abortion.

This paper draws upon qualitative data from a pluralistic evaluation of the Lothian Emergency Contraception Study to describe how the project operated in practice and to explain why enough women at risk of abortion may not have received advance supplies.

## Methods

A case study research design was used. Case study sites were ten general practices in Lothian purposively sampled to represent a range of socio-economic characteristics, locations and initial enthusiasm for the Lothian Emergency Contraception Project among professionals, and the central family planning clinic in Lothian, Scotland.

*Semi-structured interviews with health professionals*

Staff at the case study general practices took part in interviews with one researcher (PS) between November 2000 and June 2001. A total of 44 interviews with one or more general practitioners and primary care nurses from each practice covered their views, perceptions and reported response to the Lothian Emergency Contraception Project and described the way in which the project was implemented in each practice.

*Interviews with women*

Twenty two women who had responded to a postal questionnaire survey sent to women registered with the ten case study practices, or distributed to women attending the central family planning clinic and who had also received advance supplies of emergency contraception were interviewed by PS between December 2001 and May 2002. Interviews covered views about emergency contraception, experience of accessing emergency contraception, and of having it to keep at home.

*Analysis*

All interviews were audio-taped recorded and transcribed verbatim. In order to develop and test an analytical framework, all authors read a sample of transcripts. A coding scheme was developed for each set of transcripts by first identifying broad themes within the data. These broad themes, which reflected the original research aims, were views about emergency contraception, views about the Lothian Emergency Contraception Project, experiences of asking for, offering or being offered EC and use of emergency contraception. These themes were then further interrogated to identify anticipated and emergent categories within the data[3]. The transcripts were loaded into Nvivo. PS applied the coding framework to all transcripts. Further analysis involved examining sections of interviews coded to a particular theme across the datasets using the constant comparison method[4]. Commonalities within the data between respondents and within individual respondents' accounts were identified. Deviant cases were sought and explored. For reporting purposes, professionals were assigned a professional identifier (General Practitioner (GP) or Practice Nurse (PN)) and their practice assigned a number whereas women were assigned a first name pseudonym.

## Results

The interview data from both health professionals and women provides insights into the reasons that advance supplies may not have been more widely distributed to, or targeted at women at risk of unintended pregnancy and abortion.

### *Professionals' views and experiences of the Lothian Emergency Contraception Project*

Professionals' working in case study general practices reported not only that women rarely asked for advance supplies of EC but also that they were reluctant to routinely offer women supplies. They reported that they primarily offered advance supplies to women who were consulting for emergency contraception (confirming an analysis of quantitative survey data reported elsewhere[2]). Reluctance to take a proactive approach to distribution of the packs to more women seemed to be influenced by their concerns about the potentially contradictory messages implied by the offer of advance supplies; their association of EC use with "chaotic behaviour" by women; their views about the sort of women suitable for advance supplies of EC; and the practical difficulties they encountered in making the offer in the context of routine consultations.

Knowledge that emergency contraception is less reliable than combined oral contraception and that its use requires no forward planning seemed to underlie a prevailing belief that emergency contraception is not "proper contraception". The

offer of advance supplies of EC was considered antithetical to the sort of rational and planned approach to contraception favoured by professionals. Related fears that women would overuse EC and abandon more reliable methods of contraception in favour of repeated use of EC were evident. For example:

> *"This idea of having a lot of packets to use for emergencies just in case is still a little alien. I think we'd still be preferring to help people to think more pro-actively."GP1 practice 11*

Concerns that the offer of advance supplies of EC was contradictory to the promotion of safe sexual practices and might lead to exposure to sexually transmitted infections also militated against pro-active distribution.

> *"For a number of years we have been advocating safer sex which involves barrier methods, involves condoms and one would not want to dilute that message somewhere like Edinburgh where HIV infection is still potentially a problem"*
> *GP3, practice 2*

The possibility that the offer of advance supplies might be seen as sanctioning promiscuous behaviour further concerned professionals and discouraged them from pro-active distribution.

> *" Obviously you're not going to want to be encouraging them to have a huge number – well I don't know if I'm talking professionally or whether I am talking as a human being – I certainly wouldn't advocate a huge number of sexual partners. I think also from an emotional point of view and a feeling of self worth and the sort of psychological side of things"*
> *PN practice 11*

The provision of 5 courses of EC within the project was seen to endorse repeated use of EC. However professionals often associated repeated use of emergency contraception with chaotic lifestyles and did not want to be seen to be encouraging such behaviour among women.

> *" I mean it's just they are all...sometimes you think people who are a bit scatty won't be using safe sex.. In a way a lot of people would be, to my mind, a bit chaotic in their lifestyle that are relying on it too much. I mean the occasional one whose preferred method of condoms failed, that's maybe a different matter, if they'd maybe been a bit more sensible in general but they've had a problem. But if somebody's relying on packs of the morning after pill, I think they're possibly a bit more chaotic in their outlook"*
> *GP2, practice 3*

Although epidemiological risk factors for abortion are well recognised professionals rarely acknowledged the women in their practice population as those most suitable for emergency contraception to keep at home, either because of a perceived lack of need, or a perceived inability to use advance supplies appropriately. Only one of the practices, which serves a largely student population, was proactive in writing to

women on the practice list and encouraging them to collect advance supplies. They reported doing this because they saw their practice population as not only in need of supplies of emergency contraception to keep at home because of perceived promiscuous lifestyles, but also organised enough to use supplies appropriately. Other practices justified the lack of a proactive approach by characterising their population as either not in need of emergency contraception to keep at home because of prevailing responsible and organised contraceptive use, for example:

> *"It's a very middle class practice and women here are very well aware what they should do and shouldn't do. Which is not to say they don't have accidents like everybody else and they would come along. But they're not your 15/16 year olds with the high pregnancy rate. We don't tend to get young girls who put themselves at risk, we're not that type of practice really."*
> *GP1, practice 02*

or as unsuitable for supplies to keep at home because of their chaotic lifestyles, for example:

> *"I think the women who is educated, maybe middle class I think these women are more likely to take advantage of this initiative than some of the types of people we see in this practice, who perhaps aren't as aware, who sometimes need someone to say to them this is what you should do. So I think a lot depends on the women themselves*
> *GP1, practice 3*

Professionals also raised the difficulty of introducing contraceptive issues, and especially the offer of packs of emergency contraception to keep at home, into routine general practice consultations. Some considered it inappropriate to make the offer in the context of a consultation about unrelated issues, and most found it practically difficult to do so given the time constraints (with maximum 10 minutes appointments and a waiting room full of people to see) of everyday general practice. For example:

> *"It's not the sort of thing that if someone's coming into you about a cold or a spot on their face or something, that you feel, it might not be appropriate for them, or they might not be in a sexual relationship, it might just be totally inappropriate. So it's not sort of thing that I felt was appropriate to raise" GP3, practice 5*

Despite professionals' fears that it might be inappropriate to offer advance supplies of EC to women in routine consultations, none of the professionals interviewed reported women refusing an offer of advance supplies if this was made.

***Women's views and experiences of the Lothian Emergency Contraception Project***

Although some of the women we interviewed reported surprise at the offer of 5 courses of EC, most also recognised a number of benefits of having advance supplies including convenience, saving the time (and embarrassment) of visiting the doctor, and easing of anxiety. For example this 28 year old women reports her reaction to the offer of advance supplies:

*" I was just like yeah of course because I think it's really good to have. Because I know previously where I thought 'oh no I need it', but you've got to go and make phone calls and appointments and stuff and that's more bother than it's worth really so I just thought I would take it. It's comforting to know it's there" Queenie*

Nevertheless, despite these perceived advantages women reported being reluctant to ask for supplies to keep at home. Their reluctance seemed to be influenced by their views that emergency contraception was not 'proper contraception' and they expressed misgivings that the project might mean that some women would over use emergency contraception and expose themselves to sexually transmitted infections. For example:

*"It's not going to protect you from everything. It's only going to stop you getting pregnant. I think that's the main problem if people start seeing it as contraception then you've still got all your STD's and everything else" Patricia*

Women were also concerned about being judged if they asked for EC. For example, this 29 year old women said:

*" because I think there's always an element of you feel someone is judging you. You've made a mistake, everyone always goes along and says it's a burst condom. I mean how many of that is people who aren't using anything? So there's always a sort of element of guilt, anxiety...I think anything to do with contraception things, everyone's still a bit uptight and embarrassed about it" Sandra*

Expressions of concern over being judged when they accessed EC suggests an awareness among women that EC users may be seen in a morally ambiguous light because use of EC is often associated with chaotic behaviour. Concern about being judged in this context appeared to underlie their reluctance to ask for advance supplies. If *any* use of emergency contraception places a woman in perceived moral jeopardy, it is clear that many women would find it very difficult to initiate a request for the five advance supplies included in the project pack. In consequence women worked hard in their interviews to distance themselves from those they perceived as irresponsible contraception users and to establish themselves and their use of emergency contraception as responsible. Typically this distancing involved younger women, though some women also made comparisons between their own responsible contraceptive behaviour and that of friends or acquaintances. For example this 29 year old woman said:

*"If you've got it at home ...the only people who might be encouraged to have unprotected sex are much younger people who might think 'great, I've got it at home, I can take full advantage of it'.... It wouldn't encourage me at all. I generally wouldn't have intercourse without contraception anyway. It would only really be in the event of a mistake or something like that" Ursula*

## Discussion

Several studies have drawn attention to health professionals'[5,6] and women's[7] concerns about de-regulation and repeated use of emergency contraception. Similar concerns are evident in the accounts in this study and are important in explaining the lack of impact of the Lothian Emergency Contraception Project upon abortion rates. The anomalous position [8] EC continues to hold in the contraceptive repertoire makes it very difficult for doctors and nurses to wholeheartedly encourage its use and promote advance supplies. Furthermore women perceive that *any* request for EC represents a significant threat to their moral identity. This suggests that women presenting for EC must be already highly motivated to prevent pregnancy. Women who are less highly motivated to prevent pregnancy, or have a low sense of vulnerability towards pregnancy [9], are unlikely to jeopardise their moral identity by asking for five packets of EC to take home in advance of need. Yet paradoxically such women may be more likely to use EC and prevent pregnancy if they have it to hand.

Advance provision is gaining popularity as a way to increase timely and appropriate use of emergency contraception[10,11,12]. Our findings demonstrate that imaginative ways to encourage women who are not already EC users to take supplies home are needed. Women themselves are unlikely to seek out advance supplies and need reassurance from health professionals that having advance supplies of EC is responsible behaviour; such reassurance comes from a pro-active offer of advance supplies. Therefore to reach those women most in need of EC it will be necessary for professionals to address their own concerns about emergency contraception and to be proactive in encouraging women to take packs home and share them with friends. Given concern over risk of sexually transmitted infections amongst young people, health professionals may feel happier about distributing advance supplies if condoms are included in the pack .

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